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MULTIPLE SCLEROSIS AND AMYOTROPHIC LATERAL SCLEROSIS*

Etiologic Significance of Recent Epidemiologic and Genetic Studies

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THIS paper describes the results of recent epidemiologic and genetic research in multiple sclerosis and amyotrophic lateral sclerosis. It is hoped that inferences presented here on the etiology of the two syndromes will stimulate clinical and laboratory investigations that may verify or correct these inferences.

The term "human genetics" is generally well understood; but to avoid the connotation that epidemiology relates only to communicable diseases, we refer to a modification of Maxcy's[1] definition of epidemiology as the field of science dealing with the various factors that determine the frequency, the geographic distribution and the population selectivity of a disease, an infectious process or a physiologic state in a human community.

Although multiple sclerosis and amyotrophic lateral sclerosis are mentioned as though each were a single entity, it is not implied that either is due to the action of a single agent, nor is it implied that the two disorders are necessarily related to each other. In fact, the findings presented below indicate that these two disorders of the nervous system are probably unrelated etiologically. Some of their clinical and pathological features are compared in Table 1.

MULTIPLE SCLEROSIS

Clinical and Pathological Characteristics

Multiple sclerosis is primarily a disease of young adults and apparently occurs more frequently in women. It is characterized by the development of widespread asymmetrically distributed *plaques* of demyelination in the central nervous system, with relative sparing of axis cylinders, nerve cells and interstitial tissue. Often, these lesions are perivenous. The various *plaques* are usually in different stages of development, and some may resolve during remission or progress to form disruptive scars. The development of the disease and its course in any attack are unpredictable. The mean duration from onset to death in patients who do not have a complete and permanent remission is estimated as about twenty-one years, and the immediate cause of death is frequently some complication of the multiple sclerosis, such as bronchopneumonia, pyelonephritis or septicemia.[2] Demyelinating lesions may occur in almost every part of the central nervous system, being more pronounced, as a rule, in the brain stem and spinal cord than in other parts although there is usually some involvement of the cerebrum. The cerebellar hemispheres are seldom involved. According to Adams and Kubik[3] the demyelination affects not only the fiber tracts but also the gray nuclear masses. The most common location of the demyelinating lesions within the cerebral hemispheres is the white matter adjacent to the lateral ventricles, particularly near the anterior and posterior horns. The pons, medulla and spinal cord nearly always contain lesions, and any part may be affected. Areas of the optic nerves are demyelinated in many cases. Muscle atrophy and anterior-horn-cell degeneration are rarely noted.

The resulting clinical picture depends on the site of nervous-system involvement, but the most prominent findings are those of retrobulbar neuritis, diplopia, intention tremor, nystagmus, ataxia, paresthesia, weakness of the extremities, usually with signs of pyramidal-tract damage such as absent abdominal reflexes, spasticity, hyperactive reflexes and extensor plantar responses, and disruption of excretory sphincter control.[4] The correlation of clinical manifestations and anatomic findings is discussed in the excellent work of Adams and Kubik.[3]

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Epidemiologic Characteristics

Annual and seasonal variations. There is little evidence that the frequency of multiple sclerosis has been increasing in any given area over the short period during which any reliable data are available.[5] In spite of the apparent association of the high prevalence with colder climate, as described below, there is no reliable information to show any seasonal variation of onsets or exacerbations of the disease.

Geographic distribution. Multiple sclerosis today is considered to be "one of the most common organic diseases of the central nervous system in many parts of the world."[6] However, it is rarely seen in the tropics or subtropics. No death from this cause was reported among the 500,000 inhabitants of the Hawaiian Islands from 1951 to 1953[7]; Dean[8] stated that multiple sclerosis is extremely uncommon in the Capetown, South Africa, area, and, in a recent publication, the absence of the disease among the native populations of the tropical Caroline and Mariana Islands in the Western Pacific[9] is described.

Mortality statistics were obtained from various countries in Europe in the hope that a comparison might be carried out for this paper, but unfortunately differences in terminology and coding make such comparisons difficult to evaluate. The impression persists among many neurologists that the disease is far less prevalent in the Mediterranean countries than in Scandinavia and Britain. A review of earlier geographic studies has already been presented.[2,5]

Allison and Millar[10] recently described the results of their intensive survey of multiple sclerosis in Northern Ireland. Seven hundred patients were examined; in 555 cases the disease was classified as "early" or "probable" and in 145 as "possible." The prevalence rate for the total population, based on the probable and early cases, is 40.5 per 100,000.* This is substantially identical with the rate found in Winnipeg in a similar study (Table 2).

In Canada and the northern United States, the mortality rates from multiple sclerosis are higher than those in the Southern States (Fig. 1). Intensive morbidity surveys carried out in Winnipeg, Canada, and 4 cities in the United States reveal that the prevalence rate based on reported cases is higher in the more northern cities (Table 2). In 2 of these cities, Winnipeg and New Orleans, an examination of all patients was undertaken. The "corrected prevalence rate" after this clinical review revealed that the rate in Winnipeg was more than six times as high as that in New Orleans[14] (Table 2). It is uncertain which factor can be correlated with the changed prevalence in

TABLE 1. *Prominent Clinical and Pathological Features of Multiple Sclerosis and Amyotrophic Lateral Sclerosis.*

Disease	Average Age at Onset	Usual Age Range*	Sex Prevalence	Type of Onset	Symptoms	Lesions	Course	Average Duration	Usual (Immediate) Related Cause of Death
	yr.	yr.						yr.	
Multiple sclerosis	28	15-45	Slightly more frequent in females	Insidious or acute	Variable (retrobulbar neuritis, nystagmus, ataxia, spasticity, loss of sphincter control etc.)	Disseminated demyelinating plaques (demyelination probably primary lesion)	Unpredictable (remissions & exacerbations may occur)	21	Bronchopneumonia; pyelonephritis; septicemia.
Amyotrophic lateral sclerosis	44	30-65	More frequent in males	Insidious	Progressive skeletal or bulbar muscular atrophy, weakness & wasting, with fasciculations; pseudobulbar & pyramidal-tract signs sometimes present; no loss of sensation or sphincter control.	Motor-system disease; motor-neuron & lateral-column degeneration (demyelination probably secondary to motor-cortex changes).	Progressive	3	Dysphagia, with inanition, or aspiration & bronchopneumonia

*About 90 per cent of cases.

TABLE 2. *Characteristics of the Five Communities Selected for the Investigation of Multiple Sclerosis.**

Community	Latitude	Mean January Temperature	Prevalence Ratios on Jan. 1, 1949	"Corrected Prevalence Rates" on Clinical Review
	°N.	°F.	*per 100,000 population*	*per 100,000 population*
Winnipeg	50	-3.5	42	40
Boston	42	28	41	—
Denver	40	31	38	—
San Francisco	37	50	30	—
New Orleans	30	55	13	6

*Based on Kurland & Newman[11] & Kurland & Westland.[12]

*The population of Northern Ireland in 1951 was 1,370,709. Allison and Millar[10] reported the rate as 79 per 100,000, but this was based solely on the population twenty years of age and over. Possible cases were also included in the calculation of this rate. In the studies in Canada and the United States, the prevalence rates for the probable cases were calculated only for the total population.

different latitudes, but it seems to be some climatic factor such as temperature. The disease is uncommon in the subtropical community of New Orleans, but its prevalence increases rapidly as the winter temperature becomes more severe. However, it appears to make little difference after the "cold" weather area is reached, for the rate in the community with extreme cold (Winnipeg) is similar to that of Boston or Denver or Northern Ireland.

Lest physicians seeing this statement advise their patients with multiple sclerosis to go to a warmer climate, we wish to report that in an earlier comparison,[12] the life expectancy after onset of multiple sclerosis did not differ greatly in Winnipeg and New Orleans. This suggests that once the causative factor has begun to act, it is little influenced by the change in climate. However, it has been Dean's[15] impression that patients from Great Britain who have migrated to South Africa enjoy better health there.

In none of the cities in the United States and Canada in which these studies were carried out does there seem to be any undue focalization of cases. The same statement might be made for the studies by Allison and Millar[10] in Northern Ireland. Campbell and his associates[16] reported an apparent focalization in Berkshire and Derbyshire in England and assumed that it was related to excessive lead in the soil. However, a previous publication[5] reviewed this work and pointed out that the hypothesis of lead as an etiologic factor did not fit numerous other observations of geographic distribution or occupational prevalence. Furthermore, there is the likelihood that this singular observation by Campbell and his associates[16] was a coincidental finding in an extensive postal inquiry. One interesting finding reported by these investigators — that the teeth of patients with multiple sclerosis contain more lead than the teeth of normal persons — has not, to our knowledge, been repeated elsewhere. Campbell et al.[17] also observed that multiple sclerosis in some sections of England seemed to be more frequent where swayback, a demyelinating disease of lambs, was prevalent; both conditions were regarded as possibly due to the effect of lead in the soil. Since swayback is unknown in Canada and the northern United States, where multiple sclerosis is highly prevalent, the association of these disorders in England appears to be coincidental.

Swank and his co-workers[18] have reported that in Norway multiple sclerosis is less frequent in the rural areas along the costal provinces than in the uplands. Among the many possible differences in the environment of the people of the costal and upland regions, that of a higher fat intake was selected as being correlated with the presumed higher prevalence. However, in the comparison of the diets of patients with multiple sclerosis with those of normal controls in Winnipeg,[14] it was found that the former did not consume more fat than the latter before the onset of the illness. To our knowledge no one else has provided data to support the hypothesis of fat as a causative factor.

In Turkey Mutlu[19] recently made the following comment:

> . . . [patients with multiple sclerosis] are scattered through every part of the country almost proportionally with the population. By exception, there has been only one case in seven provinces of Anatolia, in the east, where the climate is warm (subtropical) and in the southwest where the Mediterranean climate dominates . . . these seven provinces are above the isotherm of 66 F. (19 C.) and below the 37-degree parallel.

Population selectivity. The population afflicted with multiple sclerosis is correlated more with geographic location than with any racial factor. In Winnipeg no significant difference in the frequency among persons of English, French or Ukrainian descent was found.[14] In Boston the rate among both whites and Negroes

FIGURE 1. *Death Rates (per 100,000 Estimated Population) from Multiple Sclerosis in the United States and Canada in 1947 (Reproduced from Kurland[12] with the Permission of the Publishers).*

Deaths attributed to "cerebral sclerosis" are excluded. United States population (1940), distributed by age, was taken as the standard. Only the white race was included, except for 1 death of an Indian in Ontario (the total Indian population of Canada is 127,500).

was considerably higher than the corresponding rates among whites and Negroes in New Orleans.[13] The variations in prevalence according to community thus appear to be due to geographic factors and not to differences in racial susceptibility.

Aside from the tendency to a slightly higher rate in females and a slight tendency to a familial aggregation of cases, described below, the occurrence of multiple sclerosis in a community appears to be on an almost random basis within the young adult group. In the "controlled" study of multiple sclerosis by Westlund and Kurland[14] in Winnipeg, no significant difference in occupation, educational level or other measures of economic or social status could be detected, nor did the housing, sanitation, water supply, milk supply or food habits, including fat intake, differ between the affected and control groups in the same community.

The effect of pregnancy in multiple sclerosis has already been reviewed.[5] On the basis of Müller's[6] careful statistical analysis it appears that pregnancy does not increase the risk of occurrence or exacerbation of the disorder.

Multiple sclerosis is reported so rarely in the spouse of an affected person that the operation of chance seems to be a plausible explanation when conjugal cases are reported. The lack of evidence of patient-to-patient transmission of the disease argues against the role of infection as a cause.

Genetic Characteristics

Among several hundred cases reported in surveys in 5 cities in the United States and Canada, there were only 2 in which a close relative was also known to have the disease. However, no special emphasis was placed on this question in the surveys, and it is difficult to be certain whether such results are accurate. No effort was made to determine the extent of consanguinity of parents of patients. A retrospective examination of 78 case records of Minnesota residents who were seen at the Mayo Clinic with multiple sclerosis in 1952 and 1953 disclosed only 1 case of a "positive" family history. The patient, a thirty-nine-year-old farmer, reported that his paternal cousin, aged forty-two years, had had multiple sclerosis for twenty years.

Many cases of more than 1 patient with multiple sclerosis in a family are reported in the literature. The recent studies by Pratt, Compston and McAlpine[20] in England, Müller[21] in Sweden and Millar and Allison[22] in Northern Ireland described the "familial incidence" as 6.5 per cent, 3.6 per cent and 6.6 per cent, respectively. With the current prevalence of multiple sclerosis and the size of the "family" often indefinite, it is not possible to say whether such cases were reported more frequently than might have been expected by chance. Mackay,[23] in his review of the literature on this subject, did not carry out any studies of statistical probability but reached the following conclusion:

> . . . the currently available evidence strongly suggests that multiple sclerosis exhibits a familial incidence more frequently than mere chance would determine. On the other hand, multiple sclerosis is too often non-familial for a familial, constitutional factor to be its sole cause.

The deficiencies of mere retrospective and descriptive familial studies of this and other chronic neurologic disorders have been considered elsewhere.[21,23,24] Pratt and his associates[20,25] and, more recently, Müller[21] and Millar and Allison[22] were the first to attempt statistical tests appropriate to the difficult problem of evaluating the role of heredity in multiple sclerosis. Each of these investigators stressed the importance and, at times, the difficulty of eliminating "hereditary degenerative disorders," such as spinocerebellar ataxia, from the series of cases being studied.

Each of the investigators determined the ratio of affected to unaffected relatives (parents or siblings) of known patients (the propositi). Each investigator stated that about 1 of 100 siblings was affected. Pratt and his associates[20] reported about 1 of 200 parents, and Müller[21] about 1 of 300 parents affected. Although the ratios in these studies are essentially the same, the interpretations of the results by the investigators differ. Pratt et al.[20] found support for the view that a genetic factor is present, whereas Müller[21] concluded that genetic factors were not active in multiple sclerosis. The principal reason for this difference of opinion lies in the evaluation of the "expected" rate in the relatives of the patients.

Pratt, Compston and McAlpine[20] and Millar and Allison[22] compared the ratios found among relatives of propositi with the estimated prevalence based on mortality statistics (Pratt et al.) or surveys of reported cases in Northern Ireland (Millar and Allison). Pratt[26] stated that the expected prevalence in the general population in corresponding age groups was approximately 1:2000 for siblings and 1:1600 for parents and concluded that there was a significantly higher prevalence among siblings and parents of propositi than in the general population, although the actual prevalence among such relatives was low.[26]

Millar and Allison[22] also reported the "expected" prevalence rate for siblings as about 1 in 2000 and indicated that the actual frequency was five to fifteen times greater than that in the general population.

Müller,[21] on the other hand, pointed out that the methods of estimating prevalence by regional surveys of reported cases or mortality statistics can be expected to give a lower rate than those of examining each individual in the community, which is essentially the method employed in determining the prevalence in parents or siblings. However, he went on to state that "even if it is assumed that the incidence of the disease is higher among the relatives of persons with multiple sclerosis than in the general population, the difference must be so small that it constitutes no proof of the occurrence of genetic factors."

Neither Müller[21] nor Millar and Allison[22] noted any increase in consanguinity of parents of their patients over the general rate of consanguineous marriages in the same region. Pratt,[25] on the other hand, indicated that the extent of cousin marriages of parents of patients is greater than would be expected by chance.

In view of the importance of twin studies in establishing the role of heredity in a disorder like multiple sclerosis both Müller[21] and Pratt[25] referred to such studies. Müller reviewed the work of Thums in which 50 pairs of twins, at least 1 of whom had multiple sclerosis, were examined. A large group of twins was first located, and the neurologic diagnoses determined later; the group was thus free of bias in selection. All of 14 monozygotic pairs of twins and all but 1 of the pairs of the dizygotic twins were discordant so far as the occurrence of multiple sclerosis was con-

cerned. Pratt[25] collected cases from other published sources as well and reported the affection in both members of pairs of monozygotic twins in 8 cases, whereas only 1 of such a pair of twins was affected in 27 other cases. At times the monozygosity of twins is difficult to establish, and this point must be considered as a possible explanation for the fact that only 1 of a pair was affected. On the other hand, in individual or small series of cases such as those collected by Pratt, there may be a greater tendency to report cases in which both twins are affected than those in which only 1 is affected. The fact remains that discordance in monozygotic twins is of sufficient magnitude to rule out a simple genetic factor in the etiology of the disease. Although the evidence is against an ordinary infectious agent as being responsible for the disorder, other conditions in the environment common to some members of the same family may account for some of the cases of familial aggregation.

It may very well be, as Pratt[25] has suggested, that some inherited factor causes a predisposition to external factors that precipitates multiple sclerosis. To this might be added the opinion expressed by others, including Müller,[21] that multiple sclerosis may be due to more than one circumstance and that the cases in which a genetic factor seems to be present may still be indistinguishable clinically and pathologically from those in which such a factor is not recognized. The fact remains that, in spite of the admirably conceived and conducted studies described above, the role of heredity in multiple sclerosis remains uncertain.

(To be concluded)

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SEMINOMA (GERMINOMA) APPARENTLY PRIMARY IN THE ANTERIOR MEDIASTINUM

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TERATOID tumors originating in the anterior mediastinum are well known. In our experience they constitute the commonest tumor at this site. The majority are cystic and benign.[1] Morphologically, various derivatives of the three germ layers are encountered in these benign tumors, including neural tissue, skin and appendages, teeth, bone, cartilage, muscle, endothelial tissue, respiratory epithelium and pancreas.

Malignant teratomas make up a relatively small group of primary anterior mediastinal tumors. Microscopically, they exhibit fewer well differentiated structures than benign tumors do. The malignant component, as in malignant teratomas elsewhere, is usually adenocarcinoma (teratocarcinoma). These two

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groups of tumors are commonly accepted as primary in the anterior mediastinum without the necessity of more than clinical examination of the testes.

Examples of primary teratoid tumors of the anterior mediastinum, with associated choriocarcinoma, have been described in the literature. Kantrowitz[2] reported the autopsy findings in a twenty-two-year-old man who had a primary teratoma containing choriocarcinomatous elements. The superior vena cava was invaded, and both lungs were studded with nodules of choriocarcinoma. No gross evidence of metastasis was present in other organs. The testes were completely sectioned in 2-mm. blocks, and no tumors or

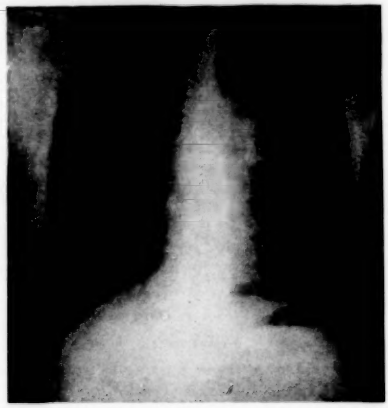

FIGURE 1. *Roentgenogram of the Chest in Case 1.*

scars were found. Additional cases of associated teratoma and choriocarcinoma of the anterior mediastinum have been reported by Ritchie,[3] by Lambert and Knox[4] and by Wilson and Cares.[5] The last three reports indicated that the testes appeared normal on routine pathological examination, but serial blocks were not made.

Choriocarcinoma of the anterior mediastinum of apparently pure type unassociated with any histologic evidence of teratoma has been reported. Arendt[6] described a tumor of the anterior mediastinum with choriocarcinomatous metastasis in lungs and liver. The testes were normal when serial sectioning was done. This case was accepted by Kantrowitz[2] as an example of primary extragenital choriocarcinoma in a male. More recently, Pugsley and Carleton[7] reported the case of a thirty-seven-year-old man from whom a tumor of the anterior mediastinum was surgically removed. The testes appeared normal on physical examination. Gonadotropic activity was found in the urine (frog test). The surgically removed specimen measured 15 cm. in diameter, was hemorrhagic and was found histologically to be a choriocarcinoma. At autopsy widespread metastasis was observed. The testes were grossly normal, weighed 20 gm. each and were completely cut into blocks in serial fashion. No tumors or scars were found.

The presence of seminomatous (germinomatous) tissue in a malignant teratoma of the anterior mediastinum has been reported by Pugsley and Carleton.[7] In this case a sixteen-year-old boy died of metastasis a month after partial surgical removal of the teratocarcinoma. At autopsy the growth was found to originate in, or adjacent to, the thymus. Although the tumor was primarily a malignant teratocarcinoma containing embryonal tissue, glands and cartilage, examination disclosed a nodule of typical seminomatous (germinomatous) structure measuring 1 cm. in diameter. The extragenital nature of this neoplasm was established by the negative results of serial blocking of both testes. It is well known that the mixture of teratocarcinoma and seminoma, as described in this case, is sometimes found in testicular tumors.[8]

To complete the spectrum of teratoid tumors and seminomas, one might expect to find examples of pure seminoma (germinoma) of the anterior mediastinum. In a discussion of the comparative morphogenesis of extragenital and gonadal teratoid tumors, Friedman[9] described 11 teratocarcinomas and 8 embryonal carcinomas of the anterior mediastinum identical with those seen in the testis. He mentioned that the pattern of germinoma (seminoma) was encountered in parts of 2 mediastinal tumors and also in the scanty tissue available from a third. In Friedman's opinion the presence of germinomatous tissue in the mediastinum makes it possible to ascribe a germinal origin to thymic (anterior mediastinal) teratoid growths.

It is the purpose of this paper to present further evidence that primary tumors of the anterior mediastinum parallel in their morphology the various tumors, either pure or mixed, found in the testis or ovary. We are presenting 3 cases of tumors that were apparently primary. Cases 1 and 2 represent seminomas (germinomas) in which the testes were normal to palpation at the time of mediastinal operation and remained free of tumor clinically during the follow-up period. Case 3 represents a primary teratocarcinoma of the anterior mediastinum that was found to contain foci of seminoma when it was sectioned into multiple blocks.

CASE REPORTS

CASE 1. A 31-year-old man complained of anorexia, loss of 13.6 kg. (30 pounds) in weight and fatigue of 8 months' duration. He had had a chronic cough for 6 years, and mild pain had been present in the left side of the thorax for 6 weeks. A mediastinal tumor was found on routine x-ray examination of the thorax several weeks before admission. On physical examination the liver edge was palpable 3 cm. below the right costal margin; both testes appeared atrophic to palpation. Roentgenograms of the thorax revealed a large lobulated mass in the anterior mediastinum on the left just above the level of the hilus (Fig. 1). Cal-

cium could not be detected in the mass. On fluoroscopic examination the mass did not pulsate, nor did it move when the patient swallowed. The esophagus was normal. Bronchoscopic examination was negative.

Excretory urography was done because of microhematuria; no abnormalities were detected. Results of subsequent urinalyses were likewise normal. Examination of the blood showed a red-cell count of 4,810,000, with a hemoglobin of 13.5 gm. per 100 cc., and a white-cell count of 3500, with a normal differential; morphologic study of the blood smear was not diagnostic. Serologic tests for syphilis were negative. The erythrocytic sedimentation rate was 18 mm. in the 1st hour (Westergren method). The blood urea nitrogen was 22 mg. per 100 cc. A liver-function test showed no retention of sulfobromophthalein. The direct serum bilirubin was 0, and the indirect was 1.3 mg. per 100 cc. The prothrombin time (Quick) was 19 seconds (normal, 17 to 19 seconds). Cytologic examinations of the sputum revealed no malignant cells. Examination of concentrated specimens of sputum did not disclose acid-fast bacilli. Tuberculin tests were negative.

A diagnosis of an indeterminate mass in the left anterior mediastinum was made, and thoracotomy was advised. At operation an extremely large tumor was found to be tightly wedged into the anterior mediastinum, extending from the sternum anteriorly to the aortic arch posteriorly and from the extreme apex of the thorax above to the pericardium below. By careful dissection the mass was removed en bloc. It was necessary to remove a portion of the pericardium to which the tumor was adherent and to open the right pleural space to get completely around the tumor.

After operation irradiation of the mediastinum was carried out. Five months after discharge pain developed in the back and hips, with a low-grade fever. Examination 6 months later disclosed a firm subcutaneous nodule over the vertex of the skull and a hard mass in the left axilla that appeared to be attached to the underlying rib. Roentgenograms showed probable osteolytic metastasis to the right femur. The testes were normal to examination. A thorough course of x-ray therapy was given to all regions of probable metastasis. The lesion of the skull disappeared almost immediately after the start of this treatment. One year later the patient had gained 9.1 kg. (20 pounds) and was feeling well. He received subsequent x-ray therapy over several regions in which pain had developed. He was last heard from 3 years after discharge, when he was working and his general health appeared to be good.

Examination of the surgical specimen revealed a well encapsulated solid tumor weighing 490 gm. and measuring 14 by 10 by 7 cm. The cut surface showed the tumor to be soft, opaque, grayish white and homogeneous, except for scattered zones of necrosis (Fig. 2). It was composed of fairly large rounded cells that were uniform in size and arranged in solid masses separated by a connective-tissue stroma, which showed a moderate degree of lymphoid infiltration (Fig. 3*A*). In addition, zones of granulomatous reaction were present in the stroma, with occasional foreign-body giant cells. The histologic appearance in all respects was that of a seminoma of the testis (Fig. 3*B*).

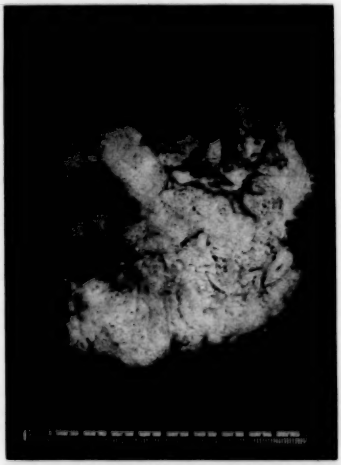

FIGURE 2. *Cut Surface of the Surgically Removed Tumor in Case 1.*
The lesion was apparently primary in the anterior mediastinum.

FIGURE 3. *Section of the Tumor Seen in Figure 1, Showing Characteristic Low-Power Seminomatous Pattern (A), with a Section of a Seminoma of the Testis for Comparison (Both, Hematoxylin and Eosin Stain X 160).*

CASE 2. A 24-year-old man came to the clinic for evaluation of a shadow first seen on a thoracic roentgenogram taken 9 months previously. Roentgenologic examination 4 years earlier on discharge from the United States Navy had been normal. The patient was entirely asymptomatic, and physical examination disclosed nothing unusual. The testes were normal to palpation.

Roentgenograms of the thorax revealed a mediastinal shadow in the region of the arch of the aorta, presenting to the left. On fluoroscopic study the shadow was seen to pulsate synchronously with the aorta and to show no appreciable movement when the patient swallowed. Results of all laboratory studies were within normal limits.

Exploratory thoracotomy was advised. The left pleural cavity was entered through the posterior periosteum of the 6th rib. The upper lobe of the left lung was extensively

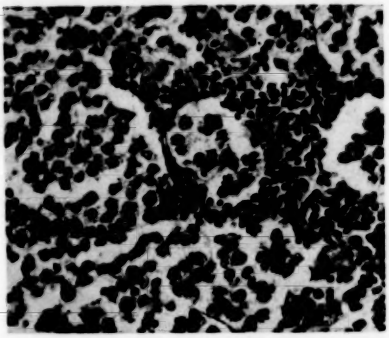

FIGURE 4. *Seminomatous Tumor, Apparently Primary in the Anterior Mediastinum in Case 2 (Hematoxylin and Eosin Stain X 280).*

The histologic pattern is that of a seminoma with lymphoid stroma.

fixed to a hard mass in the anterior mediastinum. The tumor, which extended around the aorta high up into the mediastinal cervical region along the great vessels, could not be extirpated, so that a portion of it was removed for histologic study.

The patient received a course of 13 daily x-ray treatments postoperatively. At the time of discharge the wound was entirely healed, and his general condition was satisfactory. He returned for a checkup 3½ months after operation. He felt well and had no symptoms. Roentgenograms of the thorax gave no evidence of the original mediastinal mass. On a second follow-up visit 4½ months later he complained of pain in the hips, legs and groins. A diagnosis of spondylitis was made, and he was given a course of x-ray therapy over the hips and buttocks, with benefit. Four months later, when he again returned, he was practically free of pain in the legs and hips but complained of pain in the left side of the thorax and the right knee. Roentgenologic studies of the pelvis and thorax showed nothing abnormal. Physical examination likewise disclosed nothing significant, and the cause of the pain remains obscure.

The tumor was composed of large round cells, with a moderate amount of clear or faintly staining cytoplasm; the cells were arranged in strands and masses separated by a lymphoid stroma (Fig. 4). The typical nucleus was round and hyperchromatic, containing a fairly coarse chromatin network and a prominent central nucleolus. Mitotic figures were numerous.

CASE 3. A 23-year-old man was asymptomatic except for intermittent pain under the scapular region of 1 week's duration. Roentgenologic examination of the thorax elsewhere had revealed a mediastinal tumor, and he came to the clinic for surgical treatment.

Physical examination was negative. The value for hemoglobin was 11.2 gm. per 100 cc. of blood. Results of other laboratory studies were noncontributory. Roentgenograms of the thorax showed a mass of moderate size in the left anterior mediastinum. The lung fields were clear.

Surgical exploration for an indeterminate tumor of the anterior mediastinum was carried out. A posterolateral incision was made on the left. A firm, nodular tumor that grossly resembled a thymoma was found in the anterior mediastinum. It was densely adherent and was removed with some difficulty. The tumor appeared to arise from the thymus gland, and practically the entire left lobe of the thymus was resected. A small metastatic nodule of tumor was found just behind the aorta at about the 3d interspace posteriorly. The patient was given x-ray therapy postoperatively. He died 2½ months later with signs of compression of the spinal cord.

The surgical specimen consisted of a well encapsulated tumor measuring 8 by 7 by 4.5 cm. The cut surface presented a variegated appearance, showing broad bands of

FIGURE 5. *Malignant Teratocarcinoma Primary in the Anterior Mediastinum in Case 3.*

A=teratomatous components (hematoxylin and eosin stain x 100). B=foci of seminoma with lymphoid stroma (hematoxylin and eosin stain x 160).

rather myxomatous connective tissue, islands of cartilage, multiple small cysts filled with inspissated mucoid material and zones of necrosis and hemorrhage. Histologically, the structure was that of a teratocarcinoma, with scattered zones of cartilage, embryonal connective tissue, carcinoma of glandular type and spaces lined with epithelial cells (Fig. 5*A*). In addition, study of multiple sections revealed scattered foci of seminoma with lymphoid stroma (Fig. 5*B*).

Discussion

The lesions discussed above provide evidence, in addition to that already present in the literature, that seminoma (germinoma), pure or mixed with malignant teratoma, may occur as a primary tumor of the anterior mediastinum. Pathological examination of the testes was not possible in our cases, but it is highly unlikely that the tumors described represent metastatic growth. Pathological examination of the testes by serial blocking has documented the primary nature of the tumors in certain cases of anterior mediastinal choriocarcinoma (pure), teratocarcinoma with associated choriocarcinoma and teratocarcinoma with foci of seminoma, as described above in the review of the literature. In cases of dermoids and benign teratomas of the anterior mediastinum, such pathological examination of the testes is obviously not considered necessary to exclude a primary gonadal neoplasm.

The pineal gland represents another extragonadal site for the development of teratoid and germinal tumors such as occur in the testis or ovary. The remarkable similarity, or, in fact, histologic identity of certain "pinealomas" to seminomas of the testis has frequently been noted. Russell,[10] in a carefully illustrated report on "pinealomas" of this type, pointed out that serial sections may show this tumor to be completely uniform in structure. On the other hand serial sections of some tumors may reveal a wide variety of tissues perhaps confined to a small portion of the tumor. Small foci of such nonneural tissue as mucus-secreting glands and small islands of cartilage were found in 3 of her cases. In addition she described a teratocarcinoma of the pineal body in which a "seminomatous" portion was found and a case in which a predominantly choriocarcinomatous pineal tumor contained regions resembling seminoma. On the basis of this evidence, Russell concluded that the tumor usually called "pinealoma" is in fact an atypical teratoma. Friedman,[11] in a study of 23 neoplasms of the pineal gland collected at the Armed Forces Institute of Pathology, confirmed the fact that many so-called pinealomas were identical with seminoma of the testis. He suggested an origin from primordial germ cells.

A case of primary intracranial choriocarcinoma in a fifteen-year-old boy was reported by Stowell, Sachs and Russell.[12] Autopsy revealed choriocarcinoma primary in the region of the pineal body and involving the floor of the third ventricle. Metastatic choriocarcinoma was present in all lobes of the lungs. No tumor was identified in the retroperitoneal region and the testes, which appeared normal grossly and were cut into thin slices and carefully examined without evidence of any scars or tumor. The authors expressed the opinion that the tumor arose in a preexisting teratoma of the pineal region.

It appears that the entire spectrum of "germinal" tumors (including seminoma, adult teratoma, teratocarcinoma and choriocarcinoma, pure or in various mixtures) has been represented by adequately documented examples of primary neoplasms in both the anterior mediastinum and the pineal region. A well accepted explanation is not as yet forthcoming to account for the presence of such tumors in these extragonadal sites. Schlumberger,[1] in a review of teratomas of the anterior mediastinum, outlined the various theories of genesis of these neoplasms. In his opinion teratomas of the ovary and testis are due to abnormal growth and differentiation of undifferentiated precursors of the germ cells. However, he considered extragonadal teratoid tumors to result from local dislocation of tissues during embryogenesis, teratomas of the anterior mediastinum being derived from the thymic anlage. Because of the presence of germinal tissues in tumors of both the anterior mediastinum and the pineal region, Friedman[9] doubted this theory of aberration in somatic development, preferring to regard all such lesions as arising from primordial germ cells.

It is obvious that many questions in the field of teratology, including the cells of origin and the morphologic relation of various tumors of both genital and extragenital sites, remain unanswered.

Summary

Two cases of seminoma (germinoma) apparently primary in the anterior mediastinum were studied at the Mayo Clinic. The tumor in a third case, that of a primary malignant teratoma of the anterior mediastinum, was shown on section of multiple blocks to contain foci of seminoma.

Evidence is accumulating that the entire spectrum of germinal tumors may occur in such extragonadal sites as the anterior mediastinum and the pineal region.

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CORRECTION OF THE ANEMIA OF MALABSORPTION SYNDROME (NONTROPICAL SPRUE?) BY ORAL ADMINISTRATION OF CORTISONE AND IRON*

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THE use of ACTH and cortisone in the treatment of nontropical sprue was prompted by evidence that adrenocortical insufficiency may be implicated as a factor in the etiology of the disease.[1-5] Although the role of adrenocortical hormones in intestinal absorption and in the etiology of sprue has not been established, the clinical response to corticosteroids of patients refractory to all other types of therapy has been excellent. Adlersberg et al.[6] suggest that "a functional insufficiency of the adrenal gland in patients with intractable sprue may explain the observed therapeutic effects of cortisone, hydrocortisone, and corticotrophin, while patients with Addison's disease may display features resembling those of sprue." Jones[7] has advanced the hypothesis that the corticosteroids may cause stimulation of the absorptive process characteristically reduced in the sprue syndrome. These compounds have been administered by him, not on the conviction that there was any true adrenocortical failure but "in the hope that the striking modification in intracellular activity known to be associated with corticosteroid therapy might be reflected in improved intestinal function." That intestinal absorption in patients with sprue is indeed improved by corticosteroid treatment is indicated by observations showing increased serum vitamin A concentration,[2,3,6,8] elevation of glucose tolerance curves,[5,7,9] rise in serum calcium,[2,6,8] increase in serum proteins,[2,3,7-10] return of prothrombin time to normal[3-5] and increase in chylomicron counts after fatty meals[7] during administration of ACTH or cortisone. A decrease in fecal fat has also been found,[2,3-9] although in one group this was not considered statistically significant.[4] Nitrogen loss in the stools has likewise been shown to be reduced in patients with sprue receiving hormone therapy.[3]

Improvement of the anemia has been noted in some patients[7-9] but not in others.[5] Indeed, this point has been treated superficially in most case reports reviewed, in contrast to the writings on so-called "tropical sprue," in which there has been an almost preponderant preoccupation with the hematologic response to various forms of treatment. However, Jones[7] observed hemoglobin increases in patients with intractable sprue under treatment with ACTH or cortisone, leading him to believe that "there is an effect in absorption of iron in certain cases."[11] Cooke,[5] on the other hand, found "no significant alteration in red cells, haemoglobin, or absolute values" in any of his 6 cases treated with ACTH; iron-absorption tests on 2 patients showed no changes during ACTH therapy. Neither did Taylor and his associates[3] report a significant alteration in hemoglobin or hematocrit values.

Badenoch and Callender[12] have shown, by employing radioactive iron, that patients with idiopathic steatorrhea absorb iron poorly from the gastrointestinal tract. In 13 patients studied, utilization of the oral test dose of radioactive iron was for the most part less than 2 per cent. Utilization of radioiron given intravenously was rapid and complete. Excess fat in the bowel lumen did not in itself interfere with iron absorption, as shown by excellent utilization of radioactive iron given orally to patients with steatorrhea secondary to pancreatic insufficiency and gastroenterostomy. These authors suggest that the production of apoferritin in the cells of the intestinal mucosa, as postulated by Granick,[13] may be deficient in the patient with sprue.

The effect of corticosteroid administration in correcting the anemia of the sprue patient is difficult to evaluate in many recorded cases because parenteral administration of hematinic agents was continued during the period of corticosteroid treatment. It is for this reason that the case reported below is presented. The patient had a severe degree of the malabsorption syndrome, accompanied by a hypochromic microcytic anemia that did not respond to the administration of ferrous sulfate by mouth for a three-month period. (We were assured by her family doctor that no folic acid or vitamin B_{12} was given in the four months before the institution of cortisone treatment.) Soon after cortisone was given a reticulocyte response was observed, and the anemia was corrected.

CASE REPORT

A 48-year-old housewife (S.M.H. 362603) was in good health until June, 1952, when diarrhea, characterized by 3 to 5 loose, light brown, occasionally frothy stools a day developed, and she suffered from tympanites and flatulence. She lost 5.4 kg. (12 pounds) in weight and was admitted to the Guthrie Clinic in Sayre, Pennsylvania, for study. A tentative diagnosis of sprue was made, and clinical recovery followed a series of vitamin B_{12} injections.¶ This remission lasted until December, when the symptoms recurred. Because she failed to respond to parenteral therapy with vitamin B_{12} and a dietary regimen she was referred to the Strong Memorial Hospital on June 19, 1953, having lost 9.1 kg. (20 pounds) in the previous 6 months.

The history, except for the present illness was unremark-

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¶We are indebted to Dr. Paul Shallenberger for this information.

able. Symptoms suggesting celiac disease in childhood were denied. She was menstruating regularly, without any unusual loss of blood, and there was nothing suggestive of gastrointestinal bleeding. Her life had been spent on farms in New York State.

Physical examination showed a small, extremely pale, cachectic woman who appeared older than her stated age. The weight was 35.9 kg. (79.2 pounds) and the height 1560 cm. (61.4 inches). The skin was dry and showed light-brown pigmentation over the forearms and abdomen. There was moderate presacral and pretibial edema. The tongue was smooth and pale. The liver edge was felt 1 fingerbreadth below the right costal margin. The spleen was not palpable. Neurologic, pelvic and rectal examinations revealed no abnormalities.

The blood pressure was 80/60. The other vital signs were normal.

The hemoglobin was 7.6 gm. per 100 cc. The hematocrit was 30 per cent (Wintrobe method) and the red-cell count 3,920,000. The white-cell count was 4800, with 62 per cent neutrophils, 3 per cent band forms, 33 per cent lymphocytes and 2 per cent monocytes. The red cells appeared hypochromic. There was marked anisocytosis and slight polychromatophilia, and an occasional stippled red cell was seen. The platelets appeared normal. The corrected sedimentation rate was 24 mm. in 1 hour. Reticulocyte counts were 2.7 and 1.8 per cent.

Urinalysis was unremarkable. The stools were liquid and light brown. No parasites or ova were seen. Repeated tests for occult blood were negative. Stool suspensions stained with Sudan III showed numerous droplets of neutral fat, but a quantitative fat determination was not done. Stool cultures were negative for pathogens.

Examination of the blood showed a serum albumin of 2.8 gm. and a globulin of 2.8 gm. per 100 cc. Cephalin cholesterol flocculation was ++; the prothrombin time was 60 per cent of normal. The serum cholesterol was 115 mg., the cholesterol esters 67 gm., the alkaline phosphatase 5.4 Bodansky units, and the serum amylase 56 Somogyi units (normal 30 to 150 units) per 100 cc. The serum sodium was 140 milliequiv. and the serum potassium 3.5 milliequiv. per liter. There was no bromsulfalein retention.

An oral glucose tolerance test (50 gm.) showed a fasting blood sugar of 76 mg., ½-hour value of 111 mg., 1-hour value of 127 mg., 2-hour value of 114 mg., and 3-hour value of 94 mg. per 100 cc.

Fasting vitamin A blood concentrations were low, and there was little increase after a large oral dose.

Duodenal juice was normal for trypsin, amylase and lipase activity. Gastric analysis showed free hydrochloric acid.

A posteroanterior film of the chest was normal. An upper gastrointestinal series revealed marked coarsening of the small-bowel pattern, with clumping and segmentation of the barium. A barium-enema examination was unremarkable. No loss of normal bone density was seen in the films.

During the 1st week in the hospital several unexplained temperature elevations to 102.2°F. occurred. The patient was given a high-protein, high-carbohydrate, low-fat diet, an oral multivitamin preparation (without folic acid or vitamin B_{12}) and antispasmodic drugs. She also received 2 500-cc. transfusions of whole blood. There was slight symptomatic improvement and little weight gain.

TABLE 1. *Effect of Cortisone Therapy.*

Interval after Start of Cortisone Therapy	Dosage of Cortisone	Body Weight	Hemoglobin	Hematocrit	Reticulocyte Count	Total Protein	Albumin	Globulin	Calcium	Phosphorus	Glucose Tolerance	Vitamin A Tolerance
days	*mg./day*	*kg.*	*gm./100 cc.*	*%*	*%*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		
0	0	38.6	9.2	31.0	2.1	5.4	2.3	3.1	7.5	2.2	Low	Low
20	150.0	42.8	8.9	34.5	6.0	—	—	—	—	—	—	—
34	150.0	44.9	12.3	41.0	4.6	6.5	3.5	3.0	9.5	3.0	—	—
41	100.0	45.4	13.6	43.0	4.0	—	—	—	—	—	—	—
50	100.0	46.3	12.1	42.5	1.8	—	—	—	—	—	—	—
69	75.0	50.3	—	—	—	6.6	3.5	3.1	9.1	4.2	Low	—
83	62.5	52.6	12.6	46.0	—	—	—	—	—	—	—	—
148	25.0	55.8	13.8	44.0	—	7.2	4.4	2.8	7.9	3.4	—	Low
223	37.5	55.1	15.0	46.0	—	6.7	3.8	2.9	8.4	3.1	—	—
279	37.5	55.1	13.4	45.0	—	6.5	4.1	2.4	9.1	3.0	—	—
341	37.5	57.2	14.1	44.0	—	6.7	3.6	3.1	8.8	3.3	—	—

She was discharged to the Out-Patient Department on July 11. The hemoglobin level had been raised to 11 gm. per 100 cc., and the hematocrit to 33 per cent by the transfused blood. She was advised to continue with the same regimen. In addition ferrous sulfate, 0.2 gm. 3 times a day by mouth, was prescribed.

After she had felt fairly well for 2 months loose bowel movements recurred. Ankle edema was present, and she appeared emaciated. The hemoglobin level fell to 8.4 gm. per 100 cc. despite continuous ingestion of ferrous sulfate. Her condition was deteriorating, and it was decided that cortisone therapy should be given a trial. She refused hospitalization.

Oral administration of cortisone (150 mg. daily) was started on October 22, and ferrous sulfate, 0.2 gm. 3 times a day, was continued. After 4 days of cortisone therapy there was a striking increase in appetite and sense of well-being. The patient was completely asymptomatic after 20 days. Ankle edema had disappeared by the 41st day of treatment. Weight gain and the results of serial blood studies are shown in Table 1. A reticulocyte response and a progressive rise in hemoglobin and hematocrit occurred. Improvement in the serum protein levels was noted. The prothrombin time increased to 100 per cent of normal. Serum calcium levels also rose.

A glucose tolerance test was done on the 69th day of therapy. The fasting blood sugar was 112 mg., ½-hour value 124 mg., 1-hour value 80 mg., 2-hour value 52 mg., and the 3-hour value 74 mg. per 100 cc. Analysis of a 3-day stool specimen showed that fecal fat comprised 28 per cent of the dry weight of the stool, indicating that occult steatorrhea persisted in spite of a low-fat intake.

A bone-marrow examination was repeated on the 92d day of treatment. The findings are summarized in Table 2, with remarks on the changes in the red blood cells of the peripheral blood.

Vitamin A absorption studies were again done on the 146th day. The fasting level had risen to normal, but very

little increase occurred 4½ hours after the oral dose. No improvement in the radiographic appearance of the small bowel was observed.

Clinical improvement, rise in hemoglobin and weight gain continued. The dose of cortisone was slowly decreased from 150 to 25 mg. a day (Table 1). On the 190th day of treatment diarrhea recurred, subsiding when cortisone was increased to 37.5 mg. a day. The brown skin pigmentation slowly disappeared.

The patient has continued to take 37.5 mg. of cortisone daily. On this maintenance dose she feels completely well. Ferrous sulfate has also been continued. There has been no recurrence of anemia or morphologic abnormality of red cells since cortisone was added to the iron therapy.

Discussion

This patient's anemia was primarily microcytic and hypochromic, the type said to be most common in idiopathic steatorrhea.[14] The hematologic findings suggest primarily an iron-deficiency state, although a lack of other factors responsible for normal hematopoiesis or maturation, with a resultant anemia of complex etiology, cannot be excluded (Table 2). Administration of ferrous sulfate by mouth for three months had no effect on the anemia. When cortisone was given in addition to iron, a reticulocyte response was observed, and the hemoglobin and hematocrit increased to normal. The red cells of the peripheral blood became normal in appearance, and a distinct change in the bone-marrow findings occurred. The favorable effect of cortisone may have been due, at least in part, to improved iron utilization, but in view of the studies of Badenoch and Callender[12] it seems much more likely that administration of cortisone greatly enhanced absorption of iron from the gastrointestinal tract.

Although the serum calcium and protein and the prothrombin time returned to normal, the glucose tolerance curve remained relatively flat. Fasting vitamin A concentrations increased to a normal range, but only slight improvement of vitamin A absorption curves occurred. This is in accordance with the experience of others, who have observed improvement in some but not all spheres of absorption, despite uniformly good clinical improvement.

The diagnosis of idiopathic steatorrhea seems justified in this patient on the basis of the following findings: malnutrition; diarrhea; steatorrhea; hypochromic microcytic anemia; hypoproteinemia; hypocalcemia; hypoprothrombinemia; low blood vitamin A levels and impaired absorption of vitamin A; low glucose tolerance curves; the roentgenographic appearance of the small intestine; and normal enzymatic activity of duodenal juice. The possibility of intestinal lipodystrophy (Whipple's disease) was considered; there was no indication for abdominal exploration so that such a diagnosis cannot be definitely excluded although it seems unlikely in the absence of arthritic symptoms and because the patient is a woman. The favorable response to cortisone, however, does not mediate for or against the diagnosis, since beneficial effects from ACTH and cortisone therapy have been observed in Whipple's disease[15-18] as well as in sprue. Correction of anemia, which in Whipple's disease may be due to chronic blood loss from the gastrointestinal tract,[18] is reported along with other clinical and laboratory evidence of improvement. A patient of particular interest is that of Jones et al.,[16] a forty-nine-year-old woman with the histologic changes of intestinal lipodystrophy who made a remarkable recovery with ACTH and cortisone and was in excellent health seventeen months after the start of corticosteroid therapy. In another case it was noted that the response to corticosteroids was clinically less striking than that in sprue, and a differentiation between the absorption defect in sprue and in Whipple's disease is made.[18]

Table 2. *Effect of Cortisone Therapy on the Peripheral Blood and Bone Marrow.*

Date	Peripheral Blood	Bone Marrow					
	Description	Fat	Mixed Layer	Plasma	Myeloid-Erythroid Series	Erythrocytes	Description
		%	%	%	%	%	
Before therapy: 10/22/53	About ½ of erythrocytes showed definite hypochromia; pronounced variation in size & shape, with occasional macrocytes, many target cells & rare spherocytes; minimal amount of polychromatophilia; platelets & leukocytes normal.	0.5	5	64	10	21	Somewhat hypercellular & uniformly hypertrophied in both myeloid & erythroid elements; erythropoiesis normoblastic, with myeloid-erythroid ratio of 3:1; some normoblasts showed persistence of large nucleoli & slight increase of nuclear perichromatin; many normoblasts in polychromatic stage of development slightly larger than normal; other cellular elements normal.
After 3 mo. of therapy: 1/22/54	Small number of erythrocytes appeared slightly hypochromic, with slight anisocytosis & poikilocytosis; rare target cells seen; platelets & leukocytes normal.	2.0	—	45	8	45	Slightly hypercellular, with normoblastic erythroid series; occasional macronormoblasts seen; erythropoiesis quite active, with myeloid-erythroid ratio of 2:1; other cellular elements normal.

Summary

A case of malabsorption syndrome accompanied by a hypochromic microcytic anemia, refractory to ad-

ministration of ferrous sulfate by mouth, is presented. When cortisone was added to the therapeutic regimen, the anemia was promptly corrected. Cortisone apparently promoted a marked increase in iron uptake by the cells of the intestinal mucosa.

We are indebted to Drs. Lawrence E. Young and Scott N. Swisher for their help and advice in interpreting the hematologic findings.

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COMPARISON BETWEEN WEIGHT REDUCTION ON A HIGH-CALORIE, HIGH-FAT DIET AND ON AN ISOCALORIC REGIMEN HIGH IN CARBOHYDRATE*

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With the technical assistance of Mrs. Shirley Barber and the dietary assistance of Misses I. Moen, M. Iles and A. Kerr

NEW YORK CITY

THE claim has been recently publicized that fat can be eaten ad libitum and still induce weight loss in obese subjects whereas carbohydrate in isocaloric amounts is held to stimulate the deposition of fat and hence weight gain.[1-4] The original report described losses of 4.1 to 24.5 kg. (9 to 54 pounds) in one to six months in 20 obese men on the high-fat regimen.[1] In a trial of the diet on a few patients in the Combined Endocrine Clinic of the Presbyterian Hospital the fact was confirmed that weight was lost, but the suspicion was left that the unpalatability or high-satiety value of the fat diet had resulted in a food intake well below the minimum 2870 calories recommended. Studies were therefore undertaken on patients admitted to the metabolism ward, where intake could be quantitated; the effects on weight loss of a high-fat diet providing 2870 calories daily were compared with those of an isocaloric high-carbohydrate, low-fat diet of approximately the same protein content. The weight changes with both diets were the same.

Methods

Six patients, 3 men and 3 women, were admitted to the metabolism ward for study. They were placed on weighed diets that differed among patients only in the minor details required to satisfy individual food preferences. The high-fat diet was obtained through the courtesy of Dr. A. E. Pennington and was calculated from standard tables to provide 2874 calories, with 122 gm. of protein, 242 gm. of fat and 52 gm. of carbohydrate. The baseline high-carbohydrate diet was calculated to provide 2878 calories, with 104 gm. of protein, 146 gm. of fat and 287 gm. of carbohydrate. Salt and water were given according to the Pennington[1] regimen, or to the patients' customary intake outside the hospital, when the baseline diet was being given.

Sodium and potassium contents of the urine were determined with a flame photometer. Urinary nitrogen content was measured by a modification of the Kjehldahl method. Patients were weighed daily before breakfast on a Fairbanks scale accurate to 100 gm.

Results

The first patient studied (S.G.) showed a sharp drop in weight for the first week on the Pennington regimen and a second increase in rate of weight loss relative to that on the baseline regimen in the second period on the Pennington high-fat diet (Fig. 1). This patient, however, had diarrhea in both periods on the high-fat diet. A similar early, sharp drop in

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weight occurred in the fifth patient (E.W.), who received the baseline diet initially (Fig. 2), and was associated with a considerable loss of sodium (Fig. 3).

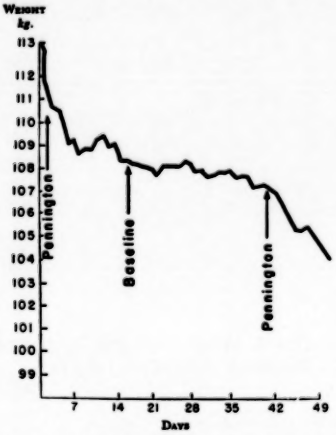

FIGURE 1. *Weight Curve of S. G., a Twenty-three-Year-Old Man.*

Note the early abrupt loss and increased rate of loss in the third diet period when the patient had diarrhea.

The second patient of the series, H.O., lost slightly during the first week on the Pennington regimen and then started a curve of slowly increasing weight. She

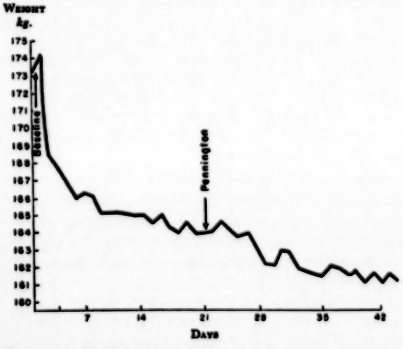

FIGURE 2. *Weight Curve of E. W., a Sixteen-Year-Old Boy, Showing the Same Abrupt Decrease in Weight on the Baseline Diet Observed in S. G. on the Pennington Diet.*

Note also the subsequent identical rate of loss of weight on high-fat and high-carbohydrate diets of isocaloric content.

gained 1 kg. in the nine days before the baseline period was begun and another 1 kg. in the next nine days.

The third patient, G.W., showed little change on the baseline diet or the Pennington diet, and the initial and final weights were the same (Fig. 4). This patient, who had had amenorrhea for six months before the experiment, had a menstrual period that began on the second day of the Pennington diet. Some retention of sodium occurred from the

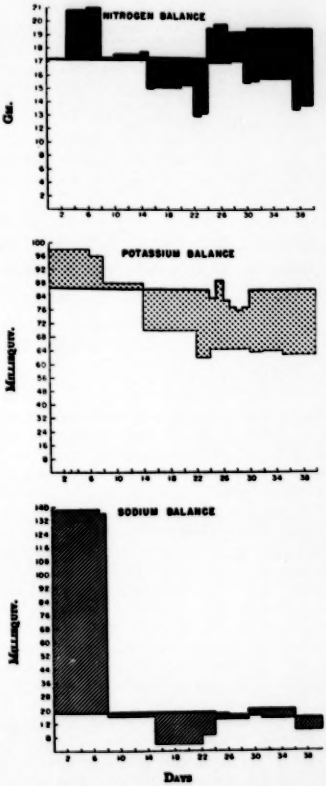

FIGURE 3. *Electrolyte and Nitrogen Balance Data, Showing Salt Dumping in the First Few Days of the Baseline Diet and Subsequent Salt Retention in E. W.*

Diet periods are the same as in those in Figure 2.

fifth to the twenty-second day of the experiment, with a slightly negative sodium balance for the next six days, after which approximate equilibrium was established (Fig. 5).

The fourth patient, A.W., also showed insignificant

fluctuations in weight. By a strange coincidence, this patient, who had been amenorrheic for a year before admission, also had a menstrual period on the second day of the Pennington regimen. Her sodium balance paralleled closely that of the preceding patient, G.W., so that the data are not presented graphically.

The last 2 patients, both men, showed a straight-line descent in the graph of the weight loss, starting after the third day of the study for D.W. and after the seventh day for E.W. (Fig. 2). The initial early, sharper decreases in weight were accompanied in both by loss of salt and water (Fig. 3). Since the data, except for the first few days, are so similar, the graphs of E.W. only are shown.

Stool Fat Analyses

Total stool fat was determined through the kindness of Dr. Dorothy Anderson, of the Babies Hospital, New York City, in 3 patients (A.W., D.W. and E.W.). Seven-day pooled specimens on the baseline and on the high-fat diets were analyzed in A.W. and E.W., and three-day and four-day pooled specimens on the two diets respectively in D.W. The maximum number of calories lost in the feces as fat was 46 daily (Table 1).

Discussion

The results of the present studies reveal that a high-fat, low-carbohydrate diet and an isocaloric

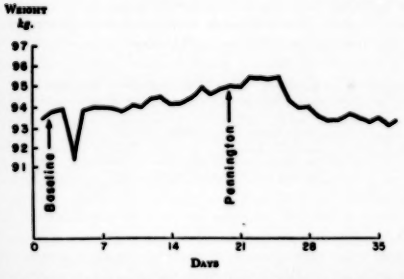

Figure 4. *Weight Curve of G. W., a Twenty-six-Year-Old Woman, Showing Weight Rise and Subsequent Fall. The patient menstruated on the second day of the Pennington regimen.*

diet high in carbohydrate and low in fat are handled similarly by the body in terms of the response of body weight. The minor differences in weight curve in the first four patients between the baseline diet and the Pennington diet periods are readily explained by salt and water shifts. The first patient had diarrhea during the period of high-fat intake; high-carbohydrate diets have been shown to cause more salt retention than low-fat diets; the third and fourth patients had menses just at the end of their initial baseline dietary periods, retaining small amounts of salt and water before the bleeding (Fig. 4 and 5) and subsequently losing the salt and water, a phenomenon known to occur in many normal women.[5] The last 2 patients, D. W. and E. W., who had uncomplicated experiments, handled the calories from both diets identically. With this conformity to classic theory, it seemed unnecessary to increase the series to document the point further.

Pennington's current hypothesis provides that carbohydrate enters the metabolic mixture but, owing

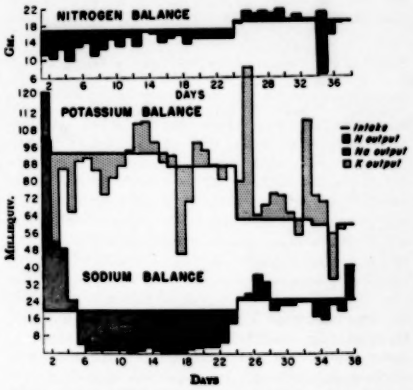

Figure 5. *Electrolyte and Nitrogen Balance in G. W., Showing Sodium Retention during the Period of Weight Gain before the Menstrual Period. Diet periods are the same as those in Figure 4.*

to an enzymatic block or defect, is not metabolized beyond the stage of pyruvic acid formation. As a consequence this metabolite accumulates and is used for fat synthesis instead of for energy purposes. Lack of energy from this source is believed to cause an increased appetite and increasing obesity until a new equilibrium is achieved at a much greater weight and food intake. At the new weight sufficient energy from glucose sources is achieved, and the obesity becomes static. At the same time fat is postulated to enter the metabolic mixture and, because it is known to be converted to glucose only to a limited extent, is held not to be used for anabolism but to become consumed in the periphery, with loss of the resultant energy as heat. The body thus continues to mobilize its own fat in the amounts normally metabolized when high-fat, low-carbohydrate diets are given, and weight loss is the result.

This theory does not take into account the fact that the enzyme systems of the body in general function reversibly. Thus, fat need not inevitably be burned but could cause fat deposition or arrest depot

fat mobilization when an excess was available. Actually, the body recognizes only carbon fragments in its metabolism and does not distinguish the original source, whether carbohydrate or fat, endogenous or exogenous.

If incoming fat were utilized only to provide heat, some mechanism to permit fat to be anabolized would ultimately have to become operative in the obese person brought to a normal weight or else he would waste away, and the successful growth and development of the Eskimo on a high-fat diet would in fact be impossible. By the same token the hypothesis that fat enters the body and is burned requires that obese people on a high-fat diet radiate more heat than those on a similar high-carbohydrate diet. However, the studies of Newburgh and Johnston[6] show clearly that the increase in heat production of obese people is only in proportion to the increase in body mass.

TABLE 1. *Fat Content of the Stools during Sample Periods on Baseline and High-Fat Diets.*

PATIENT	DIET	SAMPLE PERIOD	STOOL	
			TOTAL FAT	FAT
		days	*% of solid*	*gm./day*
A.W.	Baseline	7	19.9	3.4
	Pennington	7	33.8	5.1
D.W.	Baseline	3	24.2	4.4
	Pennington	4	27.2	5.1
E.W.	Pennington	7	42.9	3.6

An additional objection to the hypothesis that fat can be introduced into the metabolic mixture without inducing anabolism comes from the nitrogen balance data of the present study. Carbohydrate in a high-carbohydrate diet is postulated to be utilized in large part only for fat synthesis and is thus poorly available for energy output. Also, incoming fat in excess is thought not to influence the daily endogenous catabolism of fat. Thus, a reduction in the incoming fat in the diet should make little difference to the body economy. Nevertheless, essentially the same degree of negative nitrogen balance occurred with weight loss on the high-carbohydrate and high-fat diets. The retention of potassium throughout the study period in A. W. and D. W. is unexplained but suggests that the calculated figures for the potassium content of the diets may have been slightly high.

One positive feature emerges from the present studies. It is clear that some of the very obese men at least customarily take a diet with about 4000 or 5000 calories a day so that, to them, a 2800-calorie diet is a weight-reducing regimen. For example, D.W. and E.W. were in caloric equilibrium or were gaining slightly before entering the hospital. They then lost weight in the hospital on a 2870-calorie diet. The weight loss can be considered to be due to loss of fatty tissue because they remained in overall nitrogen equilibrium. Since fat tissue is approximately 10 to 20 per cent water and 80 per cent fat* 80 per cent of the weight lost was fat and hence provided 9 calories per gram. Thus, the average daily total heat output (Table 2) was 4166 and 4427 calories respectively. This much food must have been eaten to keep weight constant, and obviously more was eaten during periods of weight gain.

These figures suggest that the caloric content of the diet for reducing weight can be individualized, often at levels higher than those customarily thought of as low in calories. The use of a high-fat diet may then provide a higher satiety value than an isocaloric high-carbohydrate regimen, possibly through its unpalatability or perhaps through its effect on inhibiting gastric motility.[8] This advantage may be exploited in selected subjects without diseases that would contraindicate such an adjustment — for example, gall-bladder disease and digestive and absorptive disorders.

SUMMARY AND CONCLUSIONS

A study of the effect on weight reduction of a high-fat, low-carbohydrate diet providing 2870 calories and of an isocaloric high-carbohydrate, low-fat diet is presented.

No difference in weight loss between the 2 diets was observed in 2 male subjects; slight differences in weight loss between the diets were noted in 3 women and 1 man, but could be readily accounted for by variations in salt and water balance.

TABLE 2. *Calculated Daily Total Caloric Output of 2 Obese Patients Losing Weight Equally on Isocaloric High-Calorie Diets.*

PATIENT	AVERAGE WEIGHT LOSS	AVERAGE FAT LOSS*	AVERAGE CALORIES FROM BODY FAT	AVERAGE CALORIES FROM FOOD	AVERAGE TOTAL CALORIC OUTPUT
	gm./day	*gm./day*	*per day*	*per day*	*per day*
D.W.	180	144	1296	2874	4170
E.W.	216	173	1557	2878	4435

*See text.

Weight loss may occur with diets containing more calories than those generally considered to be low in calories; greater individualization of the caloric level employed in low-calorie regimens is suggested.

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*Newburgh et al.[7] use the figures of 10 per cent water and 90 per cent fat. The allowance for water in the present calculations was twice this to allow for the effect of variation in water content on the calculations of calories from fat sources.

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MEDICAL PROGRESS

THE MEDICAL SIGNIFICANCE OF LENTICULAR OPACITIES (CATARACT) BEFORE THE AGE OF FIFTY (Concluded)*
With Emphasis on Their Occurrence in Systemic Disorders

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Inborn metabolic errors. This heading includes the syndrome of galactosemia in infants, Wilson's disease, and a recent syndrome described by Lowe et al.[85] associated with organic aciduria. It is thought that specific metabolic defects have at least been partially identified in these particular disorders.

Galactosemia. Bruck and Rapoport[16] were the first to call attention to bilateral cataracts occurring in an infant with galactosemia. Their studies suggested an etiologic relation between the inability of the patient to metabolize galactose and the development of cataracts. Most important was the demonstration in their patient of clearing of the lenticular opacities when lactose was eliminated from the diet, a finding of considerable significance.

The essential features of the disease include failure to thrive (dating from the neonatal period), hepatomegaly, albuminuria, galactosemia and galactosuria. Evidence of liver dysfunction is usually present, and jaundice may occur. The disease is occasionally familial, and some children show mental retardation. All these symptoms and signs seem to be related to an inborn inability of the infant to metabolize galactose properly. The high lactose content in milk is thus actually poisonous to the infant, and unless the condition is recognized and milk sugar eliminated from the diet the condition is progressively one of deterioration, with failure to thrive, liver disease with cirrhosis, cataracts that are irreversible and death in early infancy. Mason and Turner[78] were the first to call this entity to the attention of the American pediatricians, but great interest in the syndrome seems to have begun after the report of Bruck and Rapoport.[16] Since 1945 many reports have appeared in the literature,[79-94] and Patz,[95] in 1952, was able to collect 27 cases from the literature. He gave his attention primarily to the occurrence of cataract and actually questioned the various authors regarding ophthalmologic findings in the individual patients. He found cataract to be extremely common when it was looked for but also found that most of the cataracts cleared if the condition was recognized in the first few months of life. Johnson[96] has stressed the fact that milk must be removed from the diet before the infants are three months old if irreversible lens opacification is to be avoided. The importance of early recognition of the disorder is obvious. The main responsibility for this must rest with the family physician or pediatrician.

Just what factors are responsible for the cataract formation in galactosemia has been the subject of brisk debate. Experimental production of cataract with high galactose feeding in rats was reported by Mitchell[97] in 1935. The studies of Bellows and Rosner[98,99] demonstrated that galactose caused a reduction in capsular permeability and glutathione content of the lens. Experiments in animals led Buschke[6] to regard changes in osmotic pressure due to the high blood and vitreous galactose levels as the most important factor. It has been well established that one can produce vacuolization of the lens by changing the osmotic pressure in the intraocular fluid. Patterson[100] believed that osmotic factors are not of primary importance and postulated that a metabolic deficiency is probably involved. He was able to prevent cataract formation in rats on high galactose intake if proper nutritional supplements were given at a time when the galactose blood levels were not excessive.

Of major importance, I believe, is the recent finding of aminoaciduria as a part of the syndrome of galactosemia. This finding was almost simultaneously described in 1952 by Bickel and Hickmans[101] and by Holzel, Komrower and Wilson.[102] More recently Gellis and his co-workers[103] studied 2 cases of galactosemia during periods of galactose administration and galactose withdrawal. They were able to show that infants with galactosemia on a galactose-free diet had a normal quantitative and qualitative pattern of amino acid excretion. After these patients had been given dietary galactose for periods of ten days

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the total excretion of alpha amino nitrogen in the urine increased greatly, and there was a notable rise in the number of amino acids excreted. Two-dimensional paper-partition chromatography showed a grossly abnormal pattern of amino acid excretion, with increased excretion of normally appearing amino acids and the appearance of threonine, tryptophane, methionine and tyrosine—amino acids that are not ordinarily found in normal urines. These workers believed that the aminoaciduria was primarily related to a direct toxic effect of galactose on the renal tubules and probably was unrelated to the action of galactose on the liver.

The experimental production of cataract in rats by tryptophane-deficient diets[6,104] or histidine-deficient diets[105] suggests that the loss of essential amino acids such as tryptophane and histidine that occurs in galactosemia may have a causal relation to cataract formation.

Wilson's disease (hepatolenticular degeneration). Lenticular changes in this disease either are extremely rare or have been largely overlooked. The Kayser–Fleischer corneal ring has been amply described and publicized as a part of the disease, but the occurrence of the so-called "sunflower cataract," resembling in all respects that which develops when a copper foreign body lodges in the lens (chalicosis lentis), has apparently not been stressed in the American literature. Thiel's[106] report in the German literature is most recent, but the characteristic cataract has been previously observed by many others.[107]

Currently, two major metabolic defects are thought to be present in Wilson's disease: an inability to transport copper in the blood owing to a low ceruloplasmin level, with accumulation of copper in the tissues; and an excessive urinary loss of amino acids and peptides.[108] The finding of typical "sunflower cataract" in this disease implies copper storage in the lens and suggests that other syndromes associated with abnormal tissue deposits (heavy metals, particularly) might show lenticular changes. This has been demonstrated in such conditions as mercurialism[109] and argyrosis,[110] but was notably absent in the cases of hemochromatosis screened by Hudson,[111] in which siderosis of the lens might have been anticipated. Significant cataracts other than those due to copper deposition are apparently not encountered in Wilson's disease. The fact that there is a marked and continuous aminoaciduria and a lack of cataracts in this disease seems to make it unlikely that aminoaciduria per se is of etiologic importance in cataractogenesis in other situations such as galactosemia. The repeated observation that experimental tryptophan cataract can only be produced in young rats before maturity is reached[104] suggests that in Wilson's disease the lack of significant cataract formation could be related to the age of the patients.

Organic aciduria. Recently, Lowe, Terrey and MacLachlan[53] described 3 infants with bilateral cataracts, specific dysfunction of the renal tubules, rickets, systemic acidosis and various physical abnormalities, including hypotonia, hyporeflexia and severe mental retardation. These children were unable to compensate for acidosis by increasing renal ammonia production and in addition had a striking organic aciduria and an abnormal amino aciduria. A case recently reported by Bickel and Thursby-Pelham[112] seems to have identical features and would constitute the fourth example of this new syndrome. As noted in the first section of this review the cases of Richards[49] and Garland[48] bear a resemblance to those of Lowe et al.[53]

This entity is undoubtedly genetically determined, and its pathogenesis is probably best explained by a primary defect of the renal tubules with associated congenital defects. The occurrence of cataract is interesting in view of the demonstration of loss of essential organic and amino acids.

Cataract Associated with Endocrine Disease

Endocrine dysfunction as a major factor in cataract formation has been repeatedly mentioned in the literature.[113] Although it has been shown that certain endocrine abnormalities are found in persons in the younger age groups with cataract,[114] there is no convincing evidence that specific endocrinopathies other than hypoparathyroidism and diabetes mellitus are related to the pathogenesis of cataract.

Cretinism and myxedema. In the literature there are many references to cataract in association with cretinism and myxedema. This seems to stem from a report of Goulden[115] in which subcapsular iridescent flakes that resembled the cataract of myotonic dystrophy were seen in 2 adult cretins who had never received thyroid replacement therapy. Buschke[6] was able to find only 5 cases in the literature with myxedema or cretinism in which cataract was reported; he stated that in view of the relative frequency of myxedema and cretinism one would expect cataract to be found more often in either of these conditions if thyroid deficiency were a primary factor. More recently, Lowe,[53] under slit-lamp visualization, examined 12 cretins over the age of twenty-six years and found flakelike opacities in 8; the opacities did not interfere with vision and were not considered to be particularly distinctive. Cataract, although occasionally found in hypothyroidism, does not seem to be in any way a constant or characteristic feature of the disorder, and there is certainly a great deal of question about its existence as a distinct entity.

Diabetes mellitus. Presenile lenticular changes in diabetes mellitus fall into two groups: transient refraction changes and true diabetic cataract formation. Transient refraction changes are a very common initial sign of diabetes (such as sudden myopia) and seem to be related in part to changes in hydration of the lens, usually stabilizing with control of the

diabetes. True diabetic cataract, on the other hand, is quite rare, and although it may regress when diabetic control is promptly instituted it can quite rapidly reach a mature, irreversible stage.

The true diabetic cataract is most often encountered in juvenile diabetes that is severe and poorly controlled. O'Brien, Molsberry and Allen[116] reported a rate of 16 per cent cataracts in 126 diabetic patients under the age of thirty-three whereas Waite and Beetham,[117] in their extensive study, mentioned a frequency of 4 per cent in 297 diabetic patients under twenty years of age, most of whom were poorly controlled and had a large daily insulin requirement. Conversely, the prevalence of cataract declines appreciably when the diabetes is adequately controlled. Joslin et al.[118] reported a rate of only 1.5 per cent in well controlled juvenile diabetes, and Marr[119] recently presented 61 cases of well controlled juvenile diabetes followed for periods up to twenty-one years in which *no* diabetic cataracts were found.

The lenticular changes that are seen in diabetes are fairly characteristic, consisting of snow-flake, milk-white cortical opacities with subcapsular vacuoles and clefts, especially in the posterior region of the lens.[120] The cataracts are often rapidly progressive, and complete bilateral opacification of the lens may occur in two or three weeks. Extremely rapid cataract formation (one to three days) may take place in very young patients, especially when the diabetes is severe.

The observation that diabetic cataract occurs when the disease is not properly controlled has naturally led to speculation regarding the pathogenesis of the lens changes. Morphologically, the cataracts of diabetes mellitus are quite similar to those produced experimentally by galactose feeding.[6] Patterson[121] was able to demonstrate a direct correlation between hyperglycemia and the development of diabetic cataract and, in a later paper,[122] showed that lowering of the blood sugar by the use of phlorizin in alloxan-diabetic rats in which insulin was withheld prevented cataract formation. This suggested that either glucose or galactose[100] might have a direct toxic effect on the lens or that the cataract formation might be related to a metabolic deficiency set up by the high blood sugar levels but not related to insulin lack per se. The exact part played by catabolism, acidosis or loss of essential nutrients (failure of synthesis) in cataract formation in uncontrolled diabetes remains to be clarified.

Hypoparathyroidism. The association of cataracts with tetany has been known for at least seventy-five years. In 1888 Landesberg[123] described a patient in whom convulsions and cataracts followed thyroidectomy. This set the stage for recognition of the association of tetany with destruction of the parathyroid glands, and this was demonstrated experimentally in 1906 by Erdheim.[124]

The relation of hypocalcemia to the development of cataract was clarified in 1930 by Kirby,[125] who concluded from his studies that lowered ionizable calcium in the blood was the major causative factor. The cataracts of hypoparathyroidism and infantile tetany, either with or without rickets, was thus rightly ascribed at that time to hypocalcemia.

Most cases of clinical hypoparathyroidism result from accidental surgical damage or removal of the parathyroid glands during the course of thyroidectomy. The disease is also encountered in an idiopathic form as well as a form associated with failure of end-organ response to parathyroid hormone, the latter being known as pseudohypoparathyroidism or the Seabright–Bantam syndrome.

Postoperative hypoparathyroidism has been reported quite often.[126-130] The idiopathic variety is much less common, but since Drake and his co-workers[131] called attention to this entity in 1939, case reports have appeared more frequently.[132-138] Steinberg and Waldron,[126] in 1952, were able to collect 52 cases at the time of their review. The signs and symptoms of the postoperative and idiopathic variety are much the same and consist mainly of changes in neuromuscular excitability, disturbances in the central nervous system and various forms of ectodermal dystrophy. Cataract is often a late sign of the disease, and the diagnosis of hypoparathyroidism is often not considered until patients have already developed this eye complication. Such an unfortunate occurrence can be avoided if this diagnosis is considered when one sees patients with epileptiform seizures, manifestations of tetany or tetanic equivalents (paresthesias, muscle stiffness and cramps) and dryness or scaly eruptions of the skin, and most particularly if the patient has had previous thyroid surgery.[129]

The cataracts are caused by the hypocalcemia rather than the lack of parathyroid hormone per se as suggested by the experimental observations of Clark.[139] The mechanism responsible for the lens changes is obscure, but most observers believe that proper control of the hypocalcemia with vitamin D or A.T. 10 therapy will prevent the formation of cataract.[136] Proper control means that the serum calcium has to be consistently kept in the normal range of 9.5 to 11 mg. per 100 cc. Latency of development is often quite striking, cataracts having been reported as late as twenty years after thyroidectomy.[126] The lenticular changes are bilateral and predominantly lamellar in type, involving the subcapsular areas of the cortical portion of the lens. The central nuclear portion of the lens is usually spared, but as lenticular damage progresses complete opacification of the lens occurs.

Pseudohypoparathyroidism was first described by Albright and his co-workers[140] in 1942, and to date approximately 26 cases have been recorded.[141] This variety of hypoparathyroidism is usually seen in young patients who have characteristics that are unique. They consist of a peculiar habitus, with short stature, rounding of the face, short stubby fingers and toes with a peculiar shortening of the metacarpal and

metatarsal bones. They present the usual features of hypoparathyroidism, including calcification of the basal ganglions and tetany with lowered serum calcium and elevated serum phosphorus, but have a complete or incomplete failure of response to parathyroid hormone (Ellsworth–Howard test). The entity is thought to be genetically determined[142] and has been observed in siblings.[143] The frequency of cataract formation is probably the same as that in the other types of hypoparathyroidism. In checking of a portion of the available case reports[140-146] regarding this point cataracts were found to be present in 4 of the 13 cases. This compares favorably with the rate of 50 per cent in patients with idiopathic hypoparathyroidism recorded by Steinberg and Waldron[138] if allowance is made for the younger age and shorter duration of the disease in the patients of this group. It is of interest that patients with brachydactyly, short stature and a congenitally small lens that becomes ectopically displaced in early life have been described.[147] This is known as the syndrome of Marchesani and is a genetically determined heredofamilial disorder. It is mentioned here only because patients with this disorder bear a marked physical resemblance to patients with pseudohypoparathyroidism.

It is obvious from the foregoing that cataract is a cardinal feature of hypoparathyroidism of any type. The finding of cataracts in young people demands that this disease be ruled out. Although it is obviously more difficult to diagnose before cataracts occur, it seems imperative for the physician to be constantly on the lookout for this disease so that irreversible damage to the lens can be avoided.

Cataract Associated with Hypocalcemia (Other than Hypoparathyroidism)

It is generally appreciated that low-calcium tetany can occur from several basic defects other than hypoparathyroidism, including a low intake of calcium and vitamin D, a failure to absorb calcium in the gut or excessive demands in the face of normal or slightly reduced intakes of calcium (as in pregnancy or lactation). In idiopathic steatorrhea failure of intestinal absorption is a major problem, and low-calcium tetany due to reduced calcium absorption frequently occurs. If the deficiency is uncorrected, osteomalacia results, and this too is quite frequent.[148] Bennett, Hunter and Vaughn,[149] in 1932, found lenticular opacities in 6 of 15 patients with severe steatorrhea, bone disease and anemia. These patients were between the ages of sixteen and forty, and all had evidence of tetany with single determinations of calcium that were either normal or low. Maxwell and Pi,[150] in 1939, presented 13 cases of osteomalacia associated with reduced serum calcium, in all of which various stages of a progressive lamellar form of cataract were observed. These patients were all females under the age of forty-one whose osteomalacia was undoubtedly secondary to pregnancy or lactation. Low-calcium tetany can occur in association with active rickets or during the healing phase when calcium is being deposited in bone.[151] Cataracts have been described both in the syndrome of infantile tetany, with or without rickets, and during the healing phase of rickets.[4]

The widespread use of vitamin D, including fortified milk and bread, has made rickets due to vitamin D deficiency a rare disease in this country. In addition, improved diagnostic and treatment measures in steatorrheal states and proper attention to the need for added calcium during pregnancy and lactation have reduced considerably the frequency of adult osteomalacia. The progress made in the prophylaxis and control of these hypocalcemic disorders undoubtedly accounts for the fact that cataract is not encountered more often. It is important to realize, however, that the chronic untreated hypocalcemia of these disorders can lead to cataract formation and loss of vision just as surely as it does in unrecognized hypoparathyroidism.

Cataract Associated with Intraocular Disease

Many local ocular disturbances can produce lenticular opacification (cataracta complicata), but it is not within the scope of this paper to discuss them in any great detail. Cataract can occur secondary to corneal injury or inflammation. Such things as perforating wounds and corneal ulcerations can lead to lens damage and opacification. Before the Credé method of prophylaxis in newborn infants cataract was commonly seen as a residuum of ophthalmia neonatorum.[152]

Diseases of the eye that lead to complicating cataract include retinitis pigmentosa, retinal detachment, absolute glaucoma, high myopia, intraocular tumor, heterochromia, iritis and iridocyclitis.[153] A point worth noting is that intraocular tumor should be suspected and ruled out in all cases of unilateral cataract, especially if glaucoma is present.[154]

Complicated cataract occurring in uveal-tract inflammation is not particularly common but does occur if the uveal disease is present over an extended period.[153] As noted above, the lens, being quite avascular, does not participate directly in the inflammatory process, and the cataract that occurs is not directly due to the inflammation. Iritis and iridocyclitis are seen in a variety of systemic disorders, including gonorrhea, syphilis, tuberculosis, sarcoidosis, the diffuse collagen diseases, including periarteritis nodosa, lupus erythematosus and dermatomyositis, rheumatoid arthritis, focal infections and many of the acute exanthematous diseases.[155-163] Although it is true that cataract complicates iritis only infrequently, Samuels[164] was able to show lenticular opacification on pathological examination of 20 lenses from enucleated globes that had been the site of severe nontraumatic iritis. One might anticipate that lenticular

opacities secondary to intraocular inflammation will become practically nonexistent now that ACTH and cortisone are available to control intraocular inflammation.

Cataract Associated with "Aortic-Arch" Syndromes

Caccamise and his associates[165,166] recently called attention to "pulseless" disease, a syndrome resulting from arterial obstruction in the great vessels of the aortic arch. This syndrome, also known as "Takayasu's disease," was originally described in 1908 in the Japanese ophthalmologic literature and apparently was considered to be primarily an ocular disorder. The occurrence of complicated cataract and the progressive appearance of anastomoses of the retinal arteriovenous loop constitute the significant ocular pathology.

Ross and McKusick,[167] in their excellent review of aortic-arch syndromes, thoroughly discussed the clinical and etiologic aspects of this entity, and Currier, DeJong and Bole[168] presented a comprehensive review of the central-nervous-system manifestations in 40 well studied cases collected from the literature. The main clinical features of the syndrome are as follows: visual symptoms, commonly dimness of vision on arising or with exercise (visual claudication); neurologic symptoms, including syncope, vertigo or light headedness on arising or with exercise, headache, paralysis, convulsions, aphasia and carotid-sinus hypersensitivity, and absence of radial pulses, with inability to obtain blood-pressure readings in the arms. The clinical findings, of course, depend on which major vessels are involved in the obliterative process.

In the 40 cases reviewed by Currier et al.[168] 15 patients had either unilateral or bilateral cataracts. The lenticular changes are undoubtedly secondary to the retinal changes, which are in turn due primarily to retinal hypoxia. The occasional observance of vessel overgrowth and retinal detachment[166] is reminiscent of the changes seen in retrolental fibroplasia, in which hypoxia seems to play a major part.

The findings of Ross and McKusick[167] suggest that syphilitic aortitis is the most common cause of the syndrome and that aneurysm need not be present. The arteritis is most probably the primary factor leading to obliteration of the vessels, and all the various causes of arteritis, including tuberculosis, Buerger's disease and periarteritis nodosa with its variants, have been mentioned as etiologic possibilities. This syndrome, then, is not a primary ocular disorder as originally described. Instead, the ocular changes are secondary to the fundamental problem of major arterial obliteration and constitute another disorder to be considered when cataract is encountered clinically.

Cataract Associated with Skin Disorders

The occasional observation of cataract in various skin diseases such as psoriasis and ichthyosis is probably due to coincidence.[6] The ophthalmologic literature often states that cataracts occur in scleroderma, but this apparently is open to question. Scleroderma is currently a well recognized clinical entity, and a recent review by Lienwand, Duryee and Richter,[169] based on a study of 150 cases, failed to reveal a single patient with significant cataract. The concept that cataracts occur in true scleroderma undoubtedly arose from the use of the word "scleroderma" in the original clinical description of the skin changes in Werner's syndrome.[59] Thannhauser[63] showed that, pathologically, skin changes of Werner's syndrome were not at all characteristic of scleroderma, and he suggested that they no longer be considered as such. It seems timely, therefore, to re-evaluate the occurrence of cataracts in scleroderma since good evidence is lacking that they actually occur.

The only skin disease that is unequivocally associated with significant cataract formation is atopic dermatitis (neurodermatitis). The occurrence of cataract in association with chronic eczema was first noted by Andogsky,[170] and many reports have appeared since the original description.[171-180] The patients characteristically have a hereditary and constitutional predisposition to hypersensitivity, often with a personal history of infantile eczema, asthma and hay fever, psychiatric maladjustment (often with marked emotional immaturity and instability), chronic eczema with remissions and exacerbations, and appearance of latent cataracts (ages twenty to twenty-five).

The cataracts, which are thought to be characteristic of the disorder, have been adequately described by Cowan and Klauder.[176] They are said to begin first in the posterior capsule of the lens, later involving the anterior subcapsular area, all the opacities apparently occurring in the cortical layer of the lens. The progression of the cataract may be rapid, and once changes have begun, they usually progress to complete lens opacification. Cowan and Klauder,[176] in a series of 100 cases of atopic dermatitis, encountered 8 in which this typical cataract was found; this figure compared favorably with the 10 per cent rate in atopic dermatitis reported by Brunsting.[172]

The cause of the cataract formation is obscure. Daniel[174] suggested that the cataracts might be related to allergic reactions in the ciliary epithelium of the eye, thus interfering with the nutrition of the lens, and proposed that the cataracts be termed "allergic cataracts." However, this concept has not received general acceptance. The fact that the cataracts are latent and do not develop until the second or third decade of life is curious, and this feature is similar to the circumstances of acquired cataract in disorders previously discussed (Table 1), in which latent development is predominant. In view of the well established occurrence of cataract due to ionizing radiation[181] and since diseases of the skin are commonly treated with x-rays, it appears worth while to investi-

gate the possibility that radiation is a factor in the development of cataracts in this disorder. They occurred unilaterally in 11 of 63 patients reported up to 1952,[176] and it is difficult to imagine, if a specific metabolic deficiency were of etiologic importance, why only one lens would be involved. The psychiatric difficulties, the presence of cataract and the dermatitis occurring in combination in this disorder make it imperative to rule out hypoparathyroidism in any new cases encountered.

Cataract Due to Poisons

Several organic solvents have been found to produce cataract when given systemically. These include naphthalene and related substances such as dinitrophenol and paradichlorobenzene.[182] Their main medical significance at present concerns the possible industrial hazard involved in working with solvents of this nature. Pike[183] reported that he was unable to produce cataract with paradichlorobenzene in laboratory animals (rabbits) and further stated that he had not encountered any evidence of toxicity or visual disturbance in human workers intimately exposed to the solvent. Experimental cataracts can consistently be produced in rabbits with naphthalene,[77] and their occurrence in man has been observed on at least one occasion.[184] Various nitrocompounds have been tested in chickens by Buschke,[185] and only a few have been found to produce lens opacities. The paucity of reports suggests that most nitrocompounds are clinically unimportant in cataractogenesis.

Dinitrophenol, a potent metabolic stimulant, was popularized as a reducing agent in the early thirties, and cataract formation was noted shortly after its introduction.[186] In 1942 Horner[187] reported delayed cataract formation in approximately 1 per cent of patients who had taken this drug therapeutically. Use of the drug clinically has been abandoned because of its toxicity, mainly in relation to cataract formation. Horner's[187] excellent summary of the problem is worthy of attention.

Ergot poisoning has been reported to produce latent cataract formation in human beings.[4] Most of these cases were reported in the Russian literature and were seen in patients who had eaten rye containing the fungus, *Claviceps purpurea*. Severe ergot poisoning, with muscular cramps and gangrene of the feet, was observed, and the cataracts were said to occur as late as five years after the poisoning. To my knowledge cataracts due to ergot poisoning have not been reported in the American literature.

Cataracts Due to Physical Agents, Including Trauma

Injury to the lens from a variety of physical causes may lead to cataract formation. Most of these physical influences are exogenous and therefore have no particular relation to underlying systemic disease. These include exogenous foreign bodies that get into the globe of the eye or lodge directly in the lens itself; direct contusive or lacerative injury of the lens; and radiation-induced lenticular changes. Although cataracts in this group are less important than those previously discussed some points seem worthy of brief mention.

When foreign bodies lodge in the eyeball or in the lens and if the capsule of the lens remains intact, gradual changes in the lens may be produced. This is especially true when toxic metals such as iron or copper-poor alloys are introduced into the eye. The resultant change in the lens with iron is quite typical (siderosis of the lens), and the changes are also quite typical with copper (chalicosis lentis — sunflower cataract).[188] The concept of *endogenous* foreign-body cataract formation is logical if one assumes that cataract might result if heavy metals were found in the ocular tissues as a part of a systemic disorder. The finding of typical sunflower cataract (chalicosis lentis) in Wilson's disease,[106] an entity known to be associated with copper deposition in the body tissues,[108] certainly supports this concept. In 1942 Atkinson[109] observed slit-lamp changes in the lens in patients with chronic mercury poisoning. The characteristic brown-colored reflex from the anterior surface of the lens that he described was later proved to be due to mercury deposits by post-mortem spectro-chemical examination of a lens that had been observed during life.[189] Recent case reports by Hunter and Lister[190] and Rosen[191] support the usefulness of this lenticular change as a diagnostic sign. Cataractous changes have also been described in systemic argyrosis, and recently cases have been reported by Rosen[192] and Bartlett.[110] As noted above, Hudson[111] was unable to find lenticular changes in hemochromatosis in which siderosis of the lens might have been anticipated. The finding of lenticular change characteristic of endogenous foreign-body reaction is thus seen to be a useful diagnostic aid. Atkinson[109] believes that changes in the lens in mercurialism is one of the earliest signs of the disease.

Cataracts due to contusive or lacerative injury to the lens have no relation to systemic disease and are included only for completeness. The excellent papers of Davidson[193,194] will be of value to those who are interested in the subject.

The various forms of radiant energy have a destructive effect on the crystalline lens. The deleterious effect of intense heat was thought to account for the cases of cataracts encountered in patients whose occupations were associated with chronic exposure to intense heat and glare. Cataracts that were reported in glass blowers,[195] iron smelters,[196] gold smelters[197] and other furnace workers[198-200] were considered by most observers to be due to infrared rays,[201] and proper measures for prophylaxis were instituted after the early descriptions. Dunn[202] recently cast doubt on this entity by not being able to find any case of cataract in a large glass-works factory in this country in which workers are regularly exposed to intense

radiant heat. The high prevalence of cataract occurring in glass blowers in the early reports from England, however, is difficult to disregard. Furthermore, the known increased frequency of cataract in the Arctic Circle and in India, as well as in farmers, supports the concept that irradiation from infrared rays of the sun is etiologically important in the production of lenticular damage.[203]

Cataract occurring after severe electric shock has been reported quite often. Adam and Klein[204] found 50 cases presented in the literature up to 1945. North[205] has pointed out that cataract is more frequent when electric burns are in the upper part of the body near to or involving the head. In most of the cases cataract was delayed for one to nineteen months after the injury.

Ionizing radiation is a most important cause of cataract formation. Clapp[206] and Milner[207] were among the first to call attention to this hazard of x-ray therapy, and both authors stressed the latent period for development of the cataracts (six months to eight years). Ham,[181] in a recent review, covered the extensive literature and emphasized the newer forms of ionizing radiation that are currently a source of concern. The occurrence of cataracts in the victims of the atomic bombing at Hiroshima[208] and in young physicists engaged in nuclear research[209] prompted the formation of a committee on radiation cataracts under the auspices of the National Research Council to study this problem, and these studies are currently in progress.

The pathogenesis of ionizing-radiation cataract is not clear, but the latest studies of Shoch and Puntney[210] suggest that the lens is damaged directly by the rays. Ham[181] points out that the human lens is quite susceptible to irradiation and that x-ray doses of over 600 r are potentially cataractogenic. This figure is important to remember if x-ray treatment in or about the face or orbit is contemplated, and it should emphasize the necessity for proper shielding of the physician's own eyes when he is using a fluoroscope.

Conclusions

This review was undertaken primarily from the point of view of the internist to assay the medical significance of cataract in the presenile age group. Because of the many systemic disorders that contribute to or are associated with cataracts the subject deserves wider attention in the general medical literature. The family physician, because of his initial contact with patients, should be familiar with the importance of this problem. Not only is knowledge of this type helpful in suggesting diagnoses but also early recognition of certain of these entities and promptness in treatment may prevent or reduce the ophthalmic complications.

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MEDICAL INTELLIGENCE

STIMULATION OF Rh ANTIBODIES IN AN Rh-NEGATIVE PATIENT WITH HEMOPHILIA

Report of a Case Developing after Repeated Transfusions of Fresh Frozen Plasma Prepared from Rh-Positive Bloods

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THE use of plasma units obtained from a single unit of whole blood is becoming more and more common for two reasons. An increasing number of hospitals prefer to use unpooled plasma because the problem of contamination of plasma pools with the virus of serum hepatitis has not yet been satisfactorily dealt with. Secondly, the 125 to 250 cc. of fresh frozen plasma given to control the clotting defect in hemophilia is most conveniently obtained from a single unit of whole blood.

This increase in the use of single-donor plasma brings up the question of the importance of matching the ABO group and Rh type of the plasma donor and the recipient. It is generally agreed that recipients of single-donor plasma should receive plasma of their own ABO group. The reason for this is twofold: anti-A and anti-B antibodies can be expected to produce some hemolysis of the recipient's red cells if ABO incompatibility exists between the plasma and the recipient; and A and B blood-group antigens are present in plasma of the corresponding group. These substances may eventually produce unwanted stimulation of immune anti-A or anti-B antibodies, or both, in recipients of incompatible ABO groups.

The situation is different so far as the Rh system is concerned. With rare exceptions[1,2] Rh antibodies are not present in plasma as naturally occurring antibodies, — that is, produced without known antigenic stimuli, — and Rh blood-group antigens have only been found in amniotic fluid,[3] never in plasma or serum. For these reasons it has been an accepted policy in many blood banks to administer plasma without considering the Rh factor. However, in the case reported below, stimulation of Rh antibodies occurred in an Rh-negative recipient receiving plasma obtained from Rh-positive donors.

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CASE REPORT

A 22-year-old man was admitted to the hospital because of hemophilia and osteogenic sarcoma of the leg. On admission the blood was found to be Group A Rh(D) negative. A screening test for blood-group antibodies, routinely performed with blood typing in this blood bank, showed that except for anti-B no antibodies were present in the patient's serum. The screening test was carried out with a red-cell pool containing all the well known blood-group antigens. The indirect Coombs test[4] and the test with trypsinized cells[5] were used.

During the first 5 months in the hospital the patient received 9 500-cc. units of blood and 67 100-cc. units of fresh frozen plasma. The 9 blood units were Group A Rh (DCE) negative. All bloods were tested for the D[u] factor[6] and found to be negative. Fresh frozen plasma was obtained from Group A and AB, Rh(D)-positive donors.

At the end of this 5-month period the serum from this patient was again tested by the screening test mentioned above. This time strong-reacting Rh antibodies of the variety anti-D+C were found in the following titers: anti-D saline antibodies, 1:32; anti-D "incomplete" antibodies, 1:256; anti-C saline antibodies, 1:8, and anti-C "incomplete" antibodies, 1:16. It was assumed at this time that the patient had been sensitized from minute amounts of Rh-positive cells that had been removed with the plasma when the units were prepared from the centrifuged fresh blood. Henceforth, he received fresh frozen plasma obtained from Rh(DCE)-negative donors only.

Titration of the anti-D and anti-C antibodies in the patient's serum was repeated 3 weeks after the 1st titrations, and the following titer values were found: anti-D saline antibodies, 0; anti-D "incomplete" antibodies, 1:2048; anti-C saline antibodies, 1:8; and anti-C "incomplete" antibodies, 1:64. The disappearance of the saline anti-D antibodies and the increase of the titer of "incomplete" antibodies showed that this patient had been under recent stimulation. Unfortunately, at this time he died of the neoplastic disease so that no further titration results could be obtained.

DISCUSSION

With plasma units obtained from one unit of blood it has generally been the accepted policy to use plasma of the same ABO group as the recipient. The basis for this policy has been that the anti-A and anti-B antibodies and the A and B blood-group antigens are present in plasma in the majority of cases. With the knowledge that this is not true for the Rh antibodies and Rh antigens it has been an accepted policy in many hospitals to disregard the Rh factor when one is dealing with plasma transfusions.

The case presented above shows that stimulation of Rh antibodies can be induced by repeated plasma transfusion, presumably because of the minute number of red cells that may be removed with plasma in the process of separation from whole blood. In this case conditions were optional for stimulation by this means. The red-cell antigens were probably well preserved in the frozen state,[7] whereas deterioration of antigens could be expected at higher storage temperature. Also, the patient had multiple, repeated doses of this presumed antigen. He may previously have been stimulated to the Rh factor by transfusions received during earlier admissions to other hospitals. Information from one outside hos-

pital revealed that he had received 3 units of Rh(D)-positive blood three years before admission. However, Rh antibodies were not demonstrable by the screening test carried out at the time of this admission.

Although this is admittedly a special case in which an unusual likelihood of such stimulation of Rh antibodies existed the potential danger of stimulation of Rh antibodies or primary Rh sensitization is present in plasma transfusions and should be considered.

Even though the stimulation of Rh antibodies as such does not create any immediate danger for the patient, the condition is undesirable in patients with this type of disease. The patients who need repeated plasma transfusions usually need multiple blood transfusions. Rh sensitization is especially dangerous in such patients since they can be expected to need blood on numerous occasions and under conditions of urgency in which errors in transfusions would be most common. In female patients the Rh sensitization might also create difficulties in subsequent pregnancies.

Summary

Repeated transfusions with fresh frozen plasma from Rh-positive donors produced stimulation of Rh antibodies in an Rh-negative patient with hemophilia and osteogenic carcinoma.

The antigenic stimulus is assumed to have arisen from minute amounts of Rh-positive red cells removed with the plasma during the processing from fresh whole blood.

It is suggested that the Rh factor as well as the ABO groups be taken into consideration when plasma is selected for transfusion to avoid unwanted Rh sensitization of the recipient.

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HIS FLAME STILL BURNS

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A HUNDRED years ago Robert Wilhelm von Bunsen, a German chemist, invented the burner that preserves his name in the mind of every student of chemistry, however elementary. It is an ironical fact that the fame of so great a scientist should depend, at least among ordinary mortals, on an invention for which according to some authorities he was not in fact responsible. Whether Farady, Desdga or Bunsen was the first to devise the method of mixing air with gas to produce the hot nonluminous flame with which everyone is familiar is immaterial today, and in any event Bunsen's other achievements were of even greater worth than the one with which his name has become permanently associated. For doctors his early work on the arsenic compounds is perhaps of special interest. This work led him to the discovery of freshly precipitated ferric oxide as an antidote to acute arsenical poisoning, and it was while he was engaged on this experiment that he lost the sight of one eye through an explosion and also became dangerously ill from arsenical poisoning.

He was a man of great practical skill and inventiveness, and there can be few who have been responsible for so many pieces of standard laboratory apparatus. Among his inventions are the filter pump, the ice calorimeter and vapor calorimeter, the grease-spot photometer, a thermostat and the carbon zinc battery. He used the last to carry out electrolytic decomposition and obtained magnesium in the metallic state for the first time. Thus, the schoolboy who loathes chemistry may at least thank Bunsen for his contribution to pyrotechnics.

Bunsen traveled widely and carried his researches into foreign lands. Having shown that in German blast furnaces 50 per cent of the fuel gas escaped unburned, he found the figure in British furnaces to be 80 per cent. His recommendations on the more efficient combustion of fuel are said to have saved millions of dollars. In Iceland he studied the thermal properties of geysers and showed by chemical analysis of Icelandic rocks how the shafts of these hot-water spouts are built up from deposited silica.

Perhaps his most fundamental contribution to chemistry was the discovery, with Kirchoff, of the method of spectrum analysis. By this means he discovered two new elements, cesium and rubidium. The manuscript of a memoir on this, the result of three years' work, was by accident burned. Bunsen, with true scientific courage, set to and repeated his labors.

He went to Heidelberg as professor of chemistry in 1852 when he was forty-one years of age. At that time the laboratories were situated in an ancient monastery. "Beneath the stone floor at our feet," Bunsen wrote, "slept the dead monks and on their tombstones we threw our waste precipitates." There was no gas in Heidelberg in those days nor any town water supply. Bunsen worked with Berzelius's spirit lamps and for water went to the pump in the yard. In spite of these conditions he soon attracted many students from Germany and elsewhere. He was entirely devoted to them, and they to him. With his own hands he showed them how best to carry out the operations on which they were engaged.

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His character was vividly described by Sir Henry Roscoe,[1] who had been his collaborator in a classic investigation on photochemical measurements and who subsequently became vice-chancellor of the University of London: "So retiring a disposition was his that it was difficult to get him to take part in public proceedings and next to impossible to induce him to make a public utterance of either a scientific or social character." He did not patent his inventions or make any profit from them. He never married, and in later life loneliness often oppressed him. Honors from his own and other countries were heaped upon him. That these counted little with him is shown by his remark to a friend who congratulated him on some particularly high distinction: "Ah! The only value such things had for me was that they pleased my mother and she is now dead." He gave up his chair in Heidelberg in 1889. Although he suffered considerably from bronchial troubles and increasing weakness he retained an active interest in scientific affairs through the years of his retirement and retained his equanimity of mind until his death in 1899 at the age of eighty-eight. His brain was examined after death and described by the pathologist Hansemann.[2] Medicine, which stands so firmly on the physical sciences, owes much to this great German chemist who, according to Roscoe,[1] was excelled by none for true modesty and greatness of heart and to his contemporaries was the *chevalier sans peur et sans reproche*.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41161

PRESENTATION OF CASE

First admission. A sixty-year-old housewife was admitted with a history of difficulty in swallowing for six to eight weeks. A barium-swallow examination showed a constricting lesion in the esophagus approximately 6 cm. in length extending inferiorly from the lower border of the sternoclavicular joint. Bronchoscopy demonstrated the tumor to be displacing the trachea but gave no evidence of invasion. An esophagectomy was performed, and a high ante-aortic esophagogastrostomy was necessary. The 9-cm. segment of resected esophagus contained at the upper end a Grade 3 squamous-cell carcinoma, which extended to about 0.5 cm. from the upper resection margin. The postoperative course was uncomplicated. Barium-swallow examination on discharge revealed a good stoma and good function.

Second admission (three months later). Unsteadiness of gait and pins-and-needles sensation in the feet had been present for about six weeks. A diagnosis of combined system disease was made, and the patient improved markedly on injections of liver extract.

Third admission (one year later). Pain around the right shoulder developed, and a small nodular mass was found above the right clavicle. X-ray films of the right shoulder and right humerus showed normal bones and joints. A needle biopsy of the mass was reported as positive for carcinoma. The patient received 2100 r to the area, with regression of the mass.

Fourth admission (six months later). A fracture of the surgical neck of the humerus resulted from a fall. She was treated with a hanging arm cast with good results.

Fifth admission (three years later). She sustained an infected compound fracture of the left wrist during a fall. The distal end of the left ulna was resected because of nonunion. Shortly after admission she became confused and disoriented and was treated for Korsakoff's syndrome. During this admission an acute gastrointestinal disorder, with a serum amylase at one point up to 135 units per 100 cc., developed. She was treated for acute pancreatitis. A gastrointestinal series showed the barium to pass promptly through the anastomosis into the thoracic portion of the stomach just above the level of the aortic arch, with no abnormalities discernible (Fig. 1).

Sixth admission (eighteen months later). An intertrochanteric fracture of the right hip followed a fall. Treatment was by a Smith-Petersen nail and plating.

Seventh admission (fourteen months later). During the previous two months the patient had about three episodes of intermittent difficulty in swallowing solid foods, each of which lasted about two days. A barium-swallow examination revealed a small amount of liquid barium outlining a distended proximal esopha-

gus with marked focal irregular narrowing at the level of the fourth thoracic vertebra and a severe obstruction to the passage of the barium. At esophagoscopy the area of stenosis was described as very hard tissue with an appearance suggesting benign stricture. A biopsy was reported as showing chronic inflammation. The stenosis was treated with bougienage.

Eighth admission (one month later). The difficulty in the swallowing of solid foods had persisted.

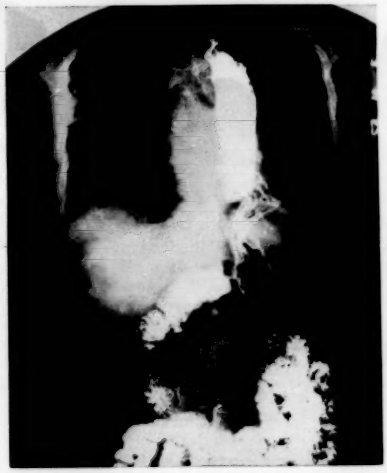

FIGURE 1. *Roentgenogram of Barium-Meal Examination. Arrow points to esophagogastric junction.*

Esophagoscopy again demonstrated a stenosis with a benign appearance. Biopsy showed chronic inflammation. The stenosed esophagus was again dilated, and the patient was placed on an esophageal diet.

Ninth admission (three months later). She sustained a fracture of the inferior ramus of the left pubis after a fall to the street. She did well with crutches.

Tenth admission (four months later). She had been swallowing well since her diet was arranged. A gastrointestinal x-ray series showed little change in the esophagus from the previous examination ten months before, but there was widening of the mediastinum, especially on the left (Fig. 2).

Final admission (ten weeks later). She had difficulty in swallowing solids and liquids of a week's duration. Regurgitation was severe.

Physical examination revealed an alert, pleasant woman in no acute distress. She weighed 76 pounds. The tongue was very dry and moderately red. The left pupil was slightly larger than the right. The skin was dry and loose. There was no supraclavicular or other significant adenopathy. Breath sounds were diminished at both lung bases, but more so on the left. There was absent tactile fremitus at the left base. There was a Grade 2 systolic murmur at the apex and base. The aortic second sound was greater than the pulmonic. The abdomen appeared disproportionately large. The liver edge was percussed 2 fingerbreadths below the right costal margin. There was a question of a mass in the right lower quadrant of the abdomen. There was no peripheral edema. Neurologic examination showed absent tendon reflexes of both ankles and the right knee and a + reflex of the left knee.

The temperature was 98.4°F., the pulse 82, and the respirations 22. The blood pressure was 85 systolic, 50 diastolic.

The urine gave a ++ test for albumin and a brown reaction for sugar. Examination of the blood

FIGURE 2. *Roentgenogram of Barium-Meal Examination Done during the Tenth Admission. Upper arrow points to narrowed area just below the stoma. Lower arrow indicates smooth indentation on the medial side of the upper part of the stomach. The stomach appears narrower than previously and does not balloon out as well.*

showed a hemoglobin of 12.8 gm. per 100 cc. and a white-cell count of 14,800, with 84 per cent neutrophils. The nonprotein nitrogen was 20 mg., the total protein 5.2 gm., the albumin 3.9 gm., and the globulin 1.3 gm. per 100 cc.

The immediate problem was one of nutrition, and the patient was maintained on fluids administered intravenously.

On the second hospital day an x-ray examination of the chest with a barium swallow showed much narrowing of the lumen of a rigid esophagus, two constricting areas, one in the proximal and the other in the distal esophagus, much widening of the mediastinum and almost complete radiopacity of the left side of the chest (Fig. 3). On the sixth hospital day

the sodium was 130 milliequiv., the potassium 5.2 milliequiv., and the chloride 100 milliequiv. per liter, and the nonprotein nitrogen 24 mg. per 100 cc. On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Chester M. Jones*: During the fifth admission the patient had an acute gastrointestinal disturbance with a serum amylase that reached a top level of 135 units per 100 cc. At the time that these determinations were made the upper limit of normal for this laboratory was between 50 and 70 units. Therefore, it was proper that she was considered to have acute pancreatitis. Conservative therapy resulted in apparent recovery.

There are certain things that I am sure of in this patient's story. She had proved squamous-cell carcinoma of the upper esophagus, for which she received proper surgical treatment with an extraordinary result. There was a metastasis to a supraclavicular lymph node on the left, which I assume was of the same type as that found in the original lesion. There was combined system disease, and she had numerous bony fractures.

I believe that the fractures were not due to metastatic disease, although no mention has been made of the x-ray interpretation of the films taken at the time of the fractures. The occurrence of bone metastases from squamous-cell esophageal cancer is unusual. Whether the nonunion of one of the fractures had anything to do with inadequate nutrition I cannot say, but I believe it had nothing to do with the original cancer.

Dr. Benjamin Castleman: The fractures were not considered pathologic.

Dr. Jones: I suppose she stumbled and fell because of combined system disease with loss of position sense.

I do not know how to interpret the term "Korsakoff syndrome." If I accept it in its literal sense, I am forced to say that she was an alcoholic. On the other hand, she did have combined system disease, there was severe trauma, and she may have had anemia. What was termed a Korsakoff syndrome may have been a temporary cerebral manifestation of that combination, or it may even have been the result of actual cerebral involvement, which occasionally occurs in combined system disease.

Seven years after the initial obstruction of the esophagus, stenosis was again noted. The question arises whether it was benign stenosis or recurrence of the original cancer. When fluoroscopy was performed a biopsy showed only chronic inflammation, but at times it is difficult to obtain adequate biopsy material in such an area of narrowing, and frequently there is inflammatory disease above an inaccessible cancer. Was the esophagoscopy done before or after bougienage?

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Dr. Edward B. Benedict: After bougienage. We always pass a bougie first.

Dr. Jones: Then I have no reason to believe that cancer was present at the time of esophagoscopy, and it is more likely that the stenosis was due to a benign stricture secondary to esophagitis. The evidence, however, does not completely rule out carcinoma, and it is quite probable that a rigid, thickened esophagus will contain cancer cells below the level of the stricture. Moreover, with an esophagogastrostomy, regurgitation frequently occurs from the stomach, with resulting peptic esophagitis. This may vary tremendously in severity. In some patients it is only of minor importance, but in others it may be very serious. The most severe form of esophagitis occurs in patients who have associated peptic ulcer. This patient apparently did not have an ulcer. Furthermore, since she had combined system disease, we can assume that, at the most, she had only a moderate amount of hydrochloric acid in the stomach, or she may have had true achlorhydria. Therefore, this stenosis probably was not a benign stricture after regurgitation of acid, with resulting peptic erosions in the esophagus. Incidentally, benign esophageal stenosis carries a fairly high percentage of associated duodenal ulcer.

Figure 3. *Roentgenogram of Barium-Meal Examination. By the time of the final admission, the stomach has become an irregularly constricted tube with stringlike narrowing at its uppermost and lowermost ends.*

Later in the course of the disease there was the x-ray finding of mediastinal enlargement. Since esophageal studies routinely include chest fluoroscopy, it is improbable that the mediastinal widening had previously been missed. This, therefore, was a new find-

ing and suggests an extension of a process that was either neoplastic or inflammatory, probably the former, although with severe chronic esophagitis there may be hilar adenopathy. There was one physical sign that I should interpret to mean an infiltrative process with nerve involvement — namely, the dilated left pupil, which had not been noted before. With combined system disease there may be cranial-nerve involvement, cerebral involvement or various types of neuritis, but I think it more reasonable in this case to assume that the superior mediastinum with its included nerves was involved by neoplasm. It is even possible that this whole picture goes back to the original squamous-cell cancer of the esophagus. I think this is the most logical diagnosis.

Is there any other possible source of a cancer that would do this? One possible source is that associated with the anacidity of combined system disease, which may predispose to gastric changes: polyp and cancer. X-ray examination of the stomach revealed no such abnormality.

The other possibility is cancer of the pancreas, although it would not readily explain the symptoms. The finding of sugar in the urine might incline one to such a possible diagnosis. However, the glycosuria may have represented simply a spill over from intravenous glucose therapy initiated because of malnutrition. The liver enlargement — if the liver was large, and there is no proof that this was so — might make me wonder about pancreatic cancer. Evidence is too slight, however, for me to stress this possibility.

Therefore, I shall say that I think this patient probably had metastatic disease from an initial squamous-cell cancer of the esophagus, which was treated with unusual success. I think that there was probably involvement of the pleura, with resulting left-sided hydrothorax. The operation that was performed, I assume, was not on the esophagus. It is conceivable that radical esophageal surgery was done, but I believe that the very poor nutritional state of the patient would probably have precluded such a procedure. The operation was presumably a palliative procedure, either a gastrostomy or jejunostomy for feeding purposes.

DR. CASTLEMAN: Should you like to see the x-ray films?

DR. JONES: Very much.

DR. JOHN F. GIBBONS: I am glad that you said that, Dr. Jones, because I spent most of the morning sorting out these films. This group of films covers the first five admissions — a period of about four years and nine months. This overexposed film, which is one of the few that I found of the original lesion, shows a filling defect in the upper esophagus, above which there is a fluid level and a round, shelflike defect. The films made after the operation (Fig. 1) demonstrate that the stomach has been pulled up and attached at this point to the esophagus. The stoma is functioning adequately. On this particular day there was food in the stomach, which causes some of the filling defect. This is a film of the right humerus at the time the biopsy was taken from the supraclavicular lymph node on that side. The humerus looks normal then, but six months later there is an impacted fracture of the neck of the humerus, which does not appear to be pathologic. None of the subsequent fractures appear to be through pathologic bone, although there is a good deal of postmenopausal osteoporosis. There were fractured ribs at that time, and here is the fractured radius and ulna.

DR. JONES: The original cancer was very high in the esophagus, so that there could not have been much remaining esophagus after the original operation.

DR. RICHARD H. SWEET: There was a very short esophagus proximally.

DR. CASTLEMAN: It is interesting to see how elongated the stomach becomes when it is drawn up into the chest (Fig. 1).

DR. GIBBONS: These films bring us up to about two years before the final admission; at this time the stoma was still functioning. There is no evidence of an abnormality in the stomach, and the lower parts of the gastrointestinal tract look normal. Later, however, we begin to see abnormal changes in the area of the stoma. About ten weeks before the final admission there is irregular narrowing of the esophagus just below the stoma for a distance of 2 or 3 cm. (Fig. 2), and a suggestion of excess tissue above the left-main-stem bronchus, which appears to be pressing upon that bronchus. There is a small, smooth indentation on the medial side of the upper portion of the stomach that was not present previously. A lateral view reveals a tiny bulge of tissue in the mediastinum, which we have not seen before.

DR. JONES: That is the first mention of any abnormality in the stomach itself by x-ray examination.

DR. GIBBONS: The last examination shows a great deal of fluid in the left pleural cavity, enlargement of the mass, a diffuse constricting change in the upper portion of the stomach and again a constriction lower in the stomach (Fig. 3). The fluoroscopist observed that there was a stringlike narrowing in this portion. There is a homogeneous opacification of the lower part of the thorax that is probably due to solid tissue or to more fluid or both.

DR. JONES: I should like to make an additional remark in view of these comments. It seems to me that there is justification for changing the diagnosis somewhat because on these x-ray films there is evidence of change in the stomach itself, which was not mentioned in the protocol. Actually this was a high thoracic stomach, with very little esophagus remaining. Dr. Sweet will correct me on that later.

DR. GIBBONS: I am not sure that there is an intrinsic narrowing.

DR. JONES: Nevertheless, it is not normal.

DR. GIBBONS: That is correct.

DR. JONES: Furthermore, there is obviously something in the distal end of the stomach that is not normal. I still think this may be evidence of metastasis from the original cancer, but one has to include the possibility of a more unusual finding — namely, an independent primary cancer of the stomach. The patient probably had had achlorhydria for a long period with the combined system disease. Neoplastic changes are apt to develop in such a situation. I do not know how these x-ray findings can be interpreted, but the gastric changes are quite striking. When the bougies were passed I take it that they were introduced well into the stomach.

DR. BENEDICT: They entered the stomach.

DR. JONES: Did they go down to here?

DR. BENEDICT: We did not try to pass them way down there.

DR. JONES: They were only here at the pylorus.

DR. BENEDICT: That is correct.

DR. CASTLEMAN: The reason "esophagus" instead of "stomach" was stated in the protocol is that the radiologist's report called it esophagus.

DR. JONES: I do not doubt it, for it looks very much like an esophagus.

DR. FARAHE MALOOF: Do you think the bone trouble may have been related to osteomalacia?

DR. JONES: It seems to me that it is possible. The patient had been poorly nourished for a long time. When she was operated on she must have been about seventy years of age. She was sixty-two when she first came in.

DR. WILLIAM V. MCDERMOTT, JR.: There is some additional information; this woman was an alcoholic. That played a role in a number of the fractures and, I suppose, also helped in the remarkable adaptation to this series of misfortunes.

DR. JONES: In other words, the statement that she had Korsakoff's syndrome should have been taken at face value. If that is true, there were many factors that would contribute to bony changes. She had malnutrition, she was postmenopausal, and she had had little or no hydrochloric acid in the stomach for years. I do not know how many patients with combined system disease have complete achlorhydria but certainly a high percentage do.

DR. BERNARD M. JACOBSON: I shall just bolster your ideas by saying not only that she had combined system disease but also that pernicious anemia later developed. She was treated with liver extract and stayed on liver for about two years. Then she gave up liver, and she staggered in three years before the final admission with a hemoglobin of 9 gm. per 100 cc. and a typical pernicious-anemia smear; the anemia responded to specific therapy. She had a superimposed nutritional difficulty.

DR. JONES: She apparently had nothing suggestive of diarrhea going along with the untreated pernicious anemia. That might have contributed somewhat. I do not believe she had had an adequate calcium intake for a long time.

DR. JACOBSON: As I recall it she had remarkably good gastric function; she did not complain of indigestion much.

DR. JONES: She had a high enough alcoholic intake to keep her from complaining.

DR. MALOOF: What is the earliest time after surgery on the upper abdomen that you have seen the so-called pernicious-anemia picture develop?

DR. JONES: After total gastrectomy the picture of pernicious anemia takes years to develop. After subtotal gastrectomy it is extremely rare and also requires many years before it can be recognized. We have had 1 patient in the Gastrointestinal Clinic with a macrocytic anemia after subtotal gastrectomy, but that did not develop for many years. The type of gastric surgery employed in this particular patient should not have resulted in pernicious anemia. I believe that she had primary anemia for many years before it was finally recognized as an integral part of the picture.

DR. CASTLEMAN: Dr. Sweet certainly should be congratulated on the superb operation that he performed nine years previously. Should you like to comment, Dr. Sweet?

DR. SWEET: This was a perfectly straightforward case of high carcinoma of the esophagus that required resection. We used the method that has been evolved for that type of case. I should like to ask our medical confreres whether they think the fact that she had a resection of a large portion of the thoracic duct might have contributed in any way to the nutritional problem. It is true that the patient never complained much about the stomach. When I saw her a few months before her last admission she was having a little difficulty in swallowing, which she was inclined to blame on the fact that the old folks' home where she lived did not serve her the right food. She was getting along quite well then. However, after looking at the x-ray films and talking with her, I thought that she was beginning to suffer from pressure from lymph-node metastases rather than esophagitis. I did not get the impression that she had an esophagitis.

CLINICAL DIAGNOSES

Metastatic carcinoma to lymph nodes from previous carcinoma of esophagus.
Pernicious anemia.

DR. CHESTER M. JONES'S DIAGNOSES

Metastases to pleura from carcinoma of esophagus removed eight years previously.
Primary carcinoma of stomach.
Hydrothorax.
Combined system disease.

Anatomical Diagnoses

(Carcinoma of esophagus resected eight years previously,) with anastomotic recurrence and extension into stomach, pericardium and mediastinum and with metastases to mediastinal, retroperitoneal and bronchial lymph nodes, pleura and peritoneum.

Hemohydrothorax.

(Pernicious anemia.)

Pathological Discussion

Dr. Castleman: At the operation, which was another esophagoscopy, Dr. Benedict found recurrent squamous-cell carcinoma. Nothing further was done; the patient died four days later. At autopsy the site of the anastomosis and the entire wall of the stomach in the mediastinum was infiltrated with carcinoma. Even the distal 2 or 3 cm. of the stomach, including the pylorus, which was below the diaphragm, was infiltrated with tumor. The entire gastric wall measured about 1 cm. in thickness — a completely annular scirrhous carcinoma, such as one sees in the usual intra-abdominal carcinoma of the stomach. The cancer also invaded the distal 0.5 cm. of the esophagus. There were extensive metastases to the pleura and mediastinal lymph nodes, both accounting for the hemorrhagic fluid in each pleural cavity. The mediastinal lymph nodes were tremendous. There were metastases to the peritoneum, and I think the abdominal pain was due to a metastasis, 4 by 6 cm., that was located in the right lower quadrant overlying the iliac crest. The pancreas looked normal. There was no fibrosis and no evidence that she had ever had pancreatitis.

Dr. McDermott: That is a fascinating sidelight, Dr. Castleman. I think there was no question that she had acute hemorrhagic pancreatitis. She had a large inflammatory mass in the upper abdomen, ecchymoses in the flanks, elevated serum amylase and high fever, — the whole classic picture, — which gradually subsided and from which she recovered. We were all very much interested to learn that the pancreas was normal four years later at post-mortem examination.

Dr. Castleman: The other interesting point here is that although the biopsy showed a squamous-cell carcinoma and one of the lymph nodes showed squamous-cell carcinoma, the rest of the tumor microscopically was a very undifferentiated carcinoma of the type that may be primary in the stomach. Since one may see variations of carcinoma in a single tumor I believe that is what occurred here. I believe that there was a very low-grade recurrence of the squamous-cell carcinoma of the esophagus that remained low grade for eight years; then suddenly, for some unknown reason but as often happens with carcinoma, the tumor took on a sudden spurt, invaded the stomach and metastasized widely. I am sure that this undifferentiated carcinoma was not present all this time.

Dr. Sweet: I have operated on patients with a squamous-cell carcinoma in the esophagus and with another type coexisting in the stomach. I wonder whether this was not a primary gastric carcinoma.

Dr. Castleman: We cannot rule that out. Since we found squamous-cell carcinoma merging with this very undifferentiated carcinoma in one of the lymph nodes I believe that it was one carcinoma; I think it would be farfetched to assume that the patient had both recurrent squamous-cell carcinoma and a new carcinoma of the stomach.

Dr. Benedict: You cannot say whether it occurred in the esophagus or grew into the esophagus from a lymph node?

Dr. Castleman: It looked as though it had recurred locally in the anastomosis. This was a very high anastomosis, as high as Dr. Sweet could make it, and the surgical specimen showed just a 5-mm. margin. A year later she had a metastasis, so that I think we can be fairly sure that she had recurrent disease from the original tumor.

Dr. Jacobson: Did you examine the spinal cord?

Dr. Castleman: Unfortunately, it was not removed. Dr. Sweet, would you do the same type of operation today, or could you have gone a little higher?

Dr. Sweet: I think today we should have left a better margin above the lesion.

CASE 41162

Presentation of Case

A five-year-old girl entered the hospital because of vomiting and abdominal pain.

Four days before admission, after returning home from supper at a neighbor's house, she began to complain of abdominal pain and vomited a large amount of ingested food. During the night she was nauseated, vomited three more times and complained that her "insides hurt." The next day she remained ill, complained of abdominal pain after taking 2 or 3 ounces of fluid and continued to vomit periodically. The vomiting became cyclic in character, at hourly intervals. That night she had an episode of epistaxis and vomited the ingested blood, but otherwise the vomitus was not bloody. A pediatrician on the third day found her mildly dehydrated, and there was acetonuria. She was given sodium bicarbonate by mouth, as well as diluted orange juice and ginger ale, all without any benefit. The condition remained the same up to the time of admission. She became somewhat confused and drowsy and was very thirsty. She had no bowel movement during the entire illness. The abdomen was noted by the mother to be swollen only on the day of admission.

The child's birth was uncomplicated; she grew

and developed normally. There was a history of chicken pox, but a review of the systems was otherwise negative. There was no history of previous abdominal pains. The members of her family had had intestinal upsets with thirty-six hours of diarrhea two weeks previously.

Physical examination revealed an acutely ill, dehydrated child, with dry skin and mucous membranes. The chest was clear. Except for a Grade 1 systolic murmur at the base, the heart was normal. The abdomen was distended, and loops of dilated bowel were visible in the right upper quadrant. Peristalsis was diminished, with occasional high-pitched rushes. The abdomen was diffusely tender, but there was no spasm or rigidity.

The temperature was 100.2°F., the pulse 136, and the respirations 24. The blood pressure was 120 systolic, 86 diastolic.

Urinalysis revealed a specific gravity of 1.028, negative tests for albumin, sugar and bile, and a sediment "loaded" with urates. Examination of the blood showed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 4500, with 68 per cent mature and 8 per cent young neutrophils, 3 per cent myelocytes and 21 per cent lymphocytes. The blood pH was 7.48. The sodium was 125 milliequiv., the chloride 89 milliequiv., the potassium 5 milliequiv., and the carbon dioxide 23 milliequiv. per liter. A stool guaiac test was negative. X-ray films of the abdomen demonstrated multiple gas-distended loops of small intestine above the level of the pelvis (Fig. 1). There was no free air seen in the peritoneal cavity.

The patient was treated with fluid intravenously—mainly 10 per cent glucose in saline solution. Attempts to pass a Miller–Abbott tube were unsuccessful. Nine and a half hours after admission an operation was performed.

Differential Diagnosis

Dr. William A. Dickson*: There is a point I should like to clear up. The protocol states that the patient had no bowel movements during the entire illness, and yet in the laboratory report the stool guaiac test was said to be negative. I assume that the child had a rectal examination and that the guaiac test was done on a glove specimen.

Dr. William C. Quinby, Jr.: That was a glove specimen, and the rectal examination was within normal limits. There was a little soft stool in the rectum. Specifically, there was no area of induration, tenderness or mass.

Dr. Dickson: May I see the x-ray films?

Dr. Joseph Hanelin: The abdominal films made with the patient upright and supine showed multiple gas-distended loops of small bowel (Fig. 1) — an appearance fairly characteristic of small-bowel obstruction in the middle or lower ileum. I am unable to see any gas within bowel loops in the pelvis. The chest is clear.

Dr. Dickson: Are there any findings that suggest a space-taking mass pushing the bowel up?

Dr. Hanelin: I do not see anything that I can define as a mass.

Dr. Dickson: I was hoping that there would be some sign of displacement.

Figure 1.

Because of the history of an intestinal upset in the family, the physician who first saw the patient assumed that she too had the same upset; later it became more obvious that the intestine was obstructed, and she was hospitalized. She was then found to be dehydrated. The urine was normal, although it was concentrated. With hemoconcentration, the hemoglobin was 14 gm. per 100 cc., but there was no leukocytosis and the smear was normal. She was in mild alkalosis: she was vomiting and had lost chlorides, with compensatory sodium loss. There was no bleeding by rectum and no blood in the stool. All that quickly rules out the commonest causes of abdominal pain and upset in a five-year-old child — namely, appendicitis and intussusception. There was no griping pain, no localization of pain, no mass and no bleeding to go with intussusception.

This, then, was a benign intestinal obstruction of which the usual causes in this age group are congenital anomalies. The most likely is malrotation of the intestine, which she may have had even though in the past she had had no symptoms. The malrotation with the gastrointestinal upset may have gone on to a volvulus. I think that would fit the picture. There was no reason to assume that she had a space-

*Assistant physician to Children's Medical Service, Massachusetts General Hospital.

taking lesion or a condition that had been present for a long while and had displaced the bowel upward.

She may have had a duplication of the alimentary tract. Even though it was not felt, a cyst of the duplicated lower small bowel could have been present, and at this time of stress, with the intestinal upset, the duplicated bowel could have become blocked off and secondarily obstructed.

Mesenteric cyst is a possibility, but against it is the fact that no mass was felt, although it could have been there without being palpated. A Meckel diverticulum, with a persistent vitelline duct, on which the intestine caught, could produce a secondary volvulus, but these are very rare.

I come back to the commonest cause of obstruction, malrotation of the bowel with volvulus, as my first choice and duplication of the bowel with cysts and obstruction as my second.

DR. ROBERT L. BERG: Does the epistaxis on the day before admission bother you?

DR. DICKSON: No; a child who is vomiting and retching very often has epistaxis accompanying the vomiting. Apparently this patient bled at no other point and bled only once. Moreover, there was no associated anemia.

DR. BERG: You do not think she may have bled into a gut wall?

DR. DICKSON: If she had, I think that she would have bled elsewhere, and also would have had a guaiac-positive stool.

DR. RALPH A. ROSS: The epistaxis did not concern me because I did not know about it until later. On the other hand there was no other sign of the bleeding. Dr. Dickson has done better than I did clinically.

DR. RICHARD B. COHEN: Dr. Quinby, would you tell us the preoperative findings and opinion in this case?

DR. QUINBY: On admission the patient presented the picture of small-bowel obstruction, the diagnosis that Dr. Dickson made. The protocol quite naturally could not emphasize the fact that, two days previously and some forty-eight hours after onset of the illness, overt signs of obstruction were not found by an extremely competent observer.

Because of an early (but transient) rise in temperature to 102°F., the low white-cell count and a pulse rate of 140 per minute, I thought she must have had peritoneal contamination close to the time of admission. We set about the problems of intestinal decompression and rehydration, but the Miller–Abbott tube would not pass through the pylorus. There was definite clinical improvement during the hours of these manipulations, and the persistent peristalsis and static abdominal picture convinced me that the bowel had not perforated and that she required early operation. My preoperative diagnosis was intussusception. I thought it probably fitted the picture, which was not typical, as well as anything.

CLINICAL DIAGNOSES

Small-bowel obstruction.
Intussusception.

DR. WILLIAM A. DICKSON'S DIAGNOSIS

Malrotation of bowel, with volvulus.
?Duplication of intestines, with cyst formation.

ANATOMICAL DIAGNOSES

Gangrenous Meckel diverticulum.
Small-bowel obstruction.

PATHOLOGICAL DISCUSSION

DR. QUINBY: At operation 30 cm. proximal to the ileocecal valve there was an inflammatory mass at the

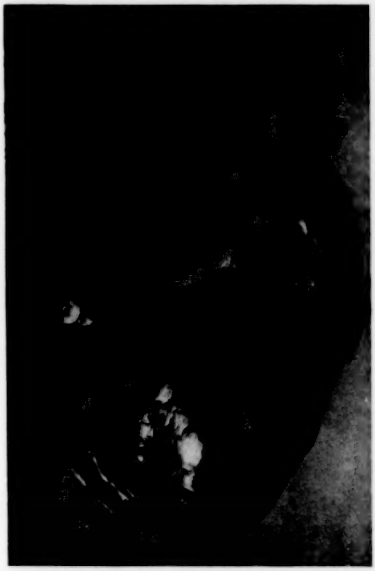


FIGURE 2.

base of the mesentery incorporating ileal loops. The distended small bowel prevented clear appraisal of the point of its obstruction, but a band about 2 mm. wide could be seen and felt at the mesenteric root. This was severed, and the involved loops were delivered through the incision; during the procedure they suddenly rotated and unscrambled themselves, with release of the obstruction. This happened so fast that I could not reconstitute the picture in my own mind, but it was obvious that there was a blue-black Meckel diverticulum about the size of my thumb with a

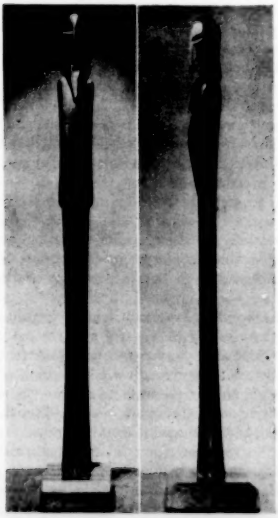
base only 1 cm. in diameter. It was not acutely inflamed but was gangrenous from infarction. It appeared that the band that I had severed was actually a vascular one, which arose from the side of the ileal mesentery at its base and led to the side and tip of the diverticulum, thus forming a bridge separate from the mesentery. It also appeared that by rotation of the diverticulum the band had tightened about its base, leaving a mark there and literally wringing its neck. A bit farther distally a short segment of ileum showed edema, redness and a 1-mm. strip of pressure necrosis of its serosa, apparently from contact with the vascular band.

DR. COHEN: The specimen was a Meckel diverticulum measuring 6 cm. in length, with a luminal diameter of 2.5 cm. It was diffusely hemorrhagic and partially gangrenous (Fig. 2).

These outpouchings of the lower ileum are remnants of the fetal omphalomesenteric canal and are usually situated 45 to 90 cm. above the ileocecal valve. They may be connected to the anterior abdominal wall in the region of the umbilicus by a fibrous band. Although the majority remain asymptomatic, a Meckel diverticulum may cause difficulty in a number of ways. It may by adhesions produce obstruction of the bowel, or, as in the case discussed today, it may itself become strangulated by adhesions. In occasional cases, when the lumen is small, it may become obstructed by food particles and develop an inflammatory reaction very much like an appendicitis. The diverticulum sometimes serves as the leading point in an intussusception. In about 25 per cent of cases a portion of the mucosa lining the diverticulum is typically gastric in type. Evidence that this ectopic mucosa is capable of peptic activity is provided by the occasional occurrence of typical peptic ulceration within the diverticulum. This is manifest clinically by abdominal pain and often bleeding.

DR. H. L. HEYL: I am not quite clear why the small bowel was obstructed.

DR. QUINBY: I wish I could answer that accurately. I believe that the diverticulum became infarcted by the process of volvulus. However, the ileum from which it sprang was virtually normal. About 3 or 4 cm. proximally and distally there were edematous short segments of bowel, and each showed a strip of serosal necrosis as though these areas had been in contact with an adhesive band. Possibly, the process in the diverticulum accounted for the first two days of symptoms, and a secondary volvulus incorporating ileum ultimately produced the full picture of obstruction. No other congenital bands were seen. The diverticulum was not attached at the umbilicus.



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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH: AN INVENTORY

EARLY in 1955 Dr. Samuel B. Kirkwood, Commissioner of Public Health of the Commonwealth of Massachusetts, released the results of an inventory of health-department activities, summarizing the achievements of 1954 and revealing plans for the future. A definite accomplishment — in deed as well as word — was the closer co-operation of the entire Department with the physicians, health agencies, hospitals and voluntary associations throughout the Commonwealth. Another step of much significance has been decentralization of departmental operations, with greater power and responsibility given district offices. The former eight districts in the State have been reduced to five, but the staffs of these districts have been augmented. The central office now sets over-all policy, with emphasis on administration, consulting, advising and technical supervision. To meet the increased burdens of the Department of Health, its four bureaus have been reconstituted as seven: Environmental Sanitation, Preventive Medicine, Health Services, Administration, Institutions, Hospital Facilities and Institute of Laboratories. The Section of Air Pollution Control was created by act of the Legislature, and the Division of Smoke Abatement, formerly in the Department of Public Utilities, was transferred to the Department of Public Health. Other activities receiving attention were the control of stream pollution, especially in the Connecticut Valley, the maintenance of standards for hospitals and, of particular importance for the steadily rising population of aged persons, the raising of standards for nursing homes. The opening of the Lemuel Shattuck Hospital for Chronic Diseases has previously been noted in the *Journal*.*

The most pressing need is now seen by Dr. Kirkwood to be an evaluation of the total health needs of the State. Such evaluations, he believes, should be made at community as well as state levels from time to time, consideration being given to the formation of regional health districts, like the Nashoba union, which is a less experimental and controversial organization than it was at its inception. Other activities conforming to public need are health education in the schools, improved measures for rehabilitation of the handicapped and aging, extension of cancer and chronic-disease control and the assurance of adequate and safe water supplies and foods. The State's institutions for medical care, which are rapidly increasing in variety and number, will, when aid is sought and if it is possible, receive financial assistance through the Hospital Survey and Construction Act. Public facilities for the aged, infirm and the chronically ill are scheduled for improvement in accordance with State and federal legislation; facilities such as tuberculosis sanatoriums, which were ade-

*Editorial. Still a worthy enterprise. *New Eng. J. Med.* 251:831, 1954.

quate in earlier years, are to be re-examined in the light of changing trends of hospitalization. The Bureau of Institutions seeks to develop a program of hospitalization co-ordinated with that of the private hospitals whereby each type of institution can assume its proper share of the over-all burden.

At the central office efforts to simplify administrative procedures further are scheduled to be extended, and training and research are to be given a more important role in the departmental program.

Few will oppose the kind of a program that Dr. Kirkwood has charted: one that seeks to find and meet the needs of the public in health matters that are not covered — and in many cases cannot be expected to be covered — by private medical and preventive medical activity. If it seems old fashioned, for example, to be overly concerned with pure water supplies in a state that has had a century's record for vision in this respect, it is only necessary to reflect on the problem posed by the disposal of radioactive wastes to make the matter timely. Likewise, it becomes more and more apparent in cities as far apart as Donora, Pennsylvania, and Los Angeles, California, that the very air that is breathed is a health heritage that can be "polluted" just as surely as the rivers and the harbors, which are none too sanitary today, despite the inventions of industry and the advances of medicine.

A forward-looking program in public health as presented by Dr. Kirkwood at the state level contains no hint of "statism" whereas it does pledge itself to come to grips with obstacles to health that are as much the concern of physicians as of their patients.

POOR RICHARD'S CATARRH

Almost one hundred and eighty-five years ago Benjamin Franklin, who was completely unfettered by any concern with hemagglutination inhibitions or complement-fixation tests for the identification of the agents of the common cold or the criteria of cytopathogenesis, pronounced as follows on this banal but costly condition: "I have long been satisfied from observation that people catch cold from one another when shut up together in close rooms and coaches, and when sitting and conversing so as to breathe each other's transpiration; the disorder being in a certain state."

A homely virtue in this observation from "Poor Richard's Almanac" is in danger of being lost in the highly scientific attempts to culture infectious agents on neoplastic Hela cells or in Roller-tube cultures of embryonic lung or skin. Such contributions as those of Andrewes and his colleagues[1] in Salisbury, England, Dingle and his co-workers[2] in Cleveland and the competent team of microbiologists at the National Institutes of Health[3] bring closer the day when the elusive viruses may be grown, harvested, frozen, emulsified, neutralized, bottled, dispersed and injected to induce immunity rather than sniffles. On the other hand, if the viruses are anywhere near as kaleidoscopic and changing as some that cause influenzal infections[4] — the milder manifestations of which are indistinguishable from those that characterize the common cold — the chances for a completely satisfactory victory are small; the prospects are better for a peaceful if sneezing coexistence.

Despite changes in methods of transportation from horse-drawn coaches to horse-drawn and then electrically driven trolley cars, Poor Richard's comment might well grace the most recent publication on the subject: people still "catch" colds and doubtless they will be "sitting and conversing so as to breathe each other's transpiration" when the jet-propelled coach finally gives way to the interplanetary rocket.

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4. Finland, M., and Barnes, M. W. Influenza B in Boston, 1952: isolations of virus and serologic studies in patients, including study of antigenic differences among influenza B viruses isolated in Boston from 1945 to 1952. *Am. J. Hyg.* 61:24-39, 1955.

LEVINE PROFESSOR

With the announcement last month that the $500,000 endowment of the Samuel A. Levine Professorship had been completed, Dean George P. Berry, of Harvard Medical School, at the same time removed the wraps from the new professor.

It is particularly appropriate that this first incumbent of the Levine Chair should be Dr. Levine's former student and long-time associate and Dr. Berry's immediate predecessor as dean of the Medical School, Dr. C. Sidney Burwell. In accepting the post Dr. Burwell caps a career as a leading investigator in the field of cardiovascular disease, as a teacher and as a kindly bedside physician. Although the professorship will by no means always be limited to any one area of human health it is also appropriate that in its incipience it will be under the direction of one who, as Dr. Levine has done, will "devote himself to the study and treatment of heart conditions and cardiovascular disease."

Dr. Burwell was born in Denver, Colorado, sixty years ago. He graduated from Allegheny College, Meadville, Pennsylvania, in 1914 and from the Harvard Medical School in 1919, then served an internship at the Massachusetts General Hospital. After this enriching experience he joined the American Red Cross Commission to West Russia, then served as a research fellow in the laboratory of Dr. Paul D. White, thus receiving his early training in cardiology at one of the very fountainheads of knowledge and of wisdom.

In 1921 he became resident physician at the Johns Hopkins Hospital and studied cardiac output under Dr. G. Canby Robinson. The year 1924 was spent in Europe; on Dr. Burwell's return he became associate professor and later professor of medicine at Vanderbilt Medical School, where he began his long-

continued studies on constrictive pericarditis. The return to Harvard Medical School took place in 1935, when Dr. Burwell became research professor of clinical medicine and dean of the School, holding the latter post until 1949, when he resigned to devote his whole time again to teaching and research.

In the picture reproduced above, although Dr. Levine occupies a somewhat superior position, Dr. Burwell is in possession of the Chair.

URGENCY AND FREQUENCY

Urologists and those dealing with urologic problems make use of a word that also applies, like its verbal companion, with frequency to many of the extraurologic urgencies of life. Almost never has this sense of urgency — of pressure and of haste — been more destructive than it is today to the effort to write reflectively, contemplatively and coherently. Whether professional writers are aware of this strain need not be questioned since presumably many of them, too, unable to retire to some remote slope of Parnassus when about to indulge in composition, must also work with a telephone at one hand and a string of importunists at the other, like that literary half-breed, the physician.

The advantages of the steel pen, the quill and the stone chisel as chirographic instruments have before this been mentioned in the literature of the subject; they defy haste, and the output of those who employed them, if small, had little excuse for not being perfect. If the inscriber of cuneiform tablets felt any urgency in the expression of his art it was that death rather than an electric buzzer might interrupt him.

No one, naturally, would assert that haste and the debasement of productive quality that results from it is any novelty, any more than one would regard promptness at meeting one's temporal obligations as inconsistent with an appreciation of spiritual and intellectual elbow room. Literature is filled with references to "time's all-devastating flight"; the plight in which the bridegroom caught the foolish virgins is a common phenomenon, and many a sundial carries on cloudy as on sunny days the admission that it is later than one thinks. All of which is no doubt necessary advice for the indolent scribe but serves mainly to increase the sour peptic juices of the conscientious one. A constant reminder that time stanchless flows, as one of the Huxleys expressed it, has a deleterious effect on those reflections that only time, and plenty of it, can ripen.

It may be that the safest way of avoiding the problem that escaping time provides is to go with the fast moving (electric) current rather than attempting to oppose it, and to accept the modern way of things entirely, regardless of its effect on the contemplative processes. Speed and power being the order of the day perhaps they should simply be used to greatest advantage and the leisurely approach left for some other phase of human existence — possibly post mortem. If the product is not so good, no one else will have time to notice the difference.

There has been, of course, plenty of experience with this increasing tempo, rendered easier, if no more desirable, by power braking and power steering. More wood can be cut with a chain saw than with a hand-drawn cross cut, let the chips fall where they may, and an electric typewriter can certainly produce a maximum of words with a minimum of pressure — at least from the fingers. A grass-cutting tool is now available powered by a gasoline motor that hangs over the shoulder, and perhaps the same principle can be applied to the fountain pen.

Still, before giving in too completely to the haste that mechanical power has made so much a part of life, one may recall the difficulties experienced by various banks and other business houses caught in the power failures that followed last autumn's hurricanes. Relying on electrically driven machines to cast up their accounts, photostat their checks, prepare their statements, lick their stamps, open their mail and perhaps read it, they succumbed as if to a

paralytic stroke when the lines went out of order. The peace that followed had some of the qualities of a vacuum, and many a junior executive, the telephone lines that bound him being torn asunder, experienced his first serious break in morale.

On the whole, the original premise seems still to be tenable, that the best creative work is not necessarily produced by authors on whose shoulders an urgent hand seems continually to be pressed.

Bibliographical Notices. An address to the Graduating Class of the Medical Department of the University of Nashville. ***By Paul F. Eve, M.D. Nashville, 1855, Pp. 22.***

The sentiments and opinions contained in this address are such as will commend it to every high-minded and conscientious member of the profession, and must have a most happy influence on the graduating class.

Boston M. & S. J., *April 26, 1855*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

POLIOMYELITIS VACCINE

The Massachusetts Department of Public Health has announced that poliomyelitis vaccine will be available without charge to first-grade and second-grade children throughout the nation. Vaccine will also be for sale, if the product is licensed.

To meet the need for guidance in its administration the Massachusetts Chapter of the American Academy of Pediatrics called together an advisory committee to suggest a program. This committee has made the following statement:

> The Committee understands that no vaccine will be released for use this year unless the release is licensed by the National Institutes of Health.
>
> The Committee understands that if the vaccine is released, the first-grade and second-grade children in all public, private and parochial schools will receive vaccine supplied without charge by the National Foundation for Infantile Paralysis.
>
> The Committee realizes that the commercial supply of vaccine available to private physicians will be insufficient for administration to all age groups during the current season.
>
> The Committee recommends that this commercial vaccine be used in the following groups: *first priority* — all kindergarten and preschool children over one year of age; *second priority* — pregnant women; and *third priority*, all school children in grades three through eight.

The Advisory Committee consists of the following members: Conrad Wesselhoeft, M.D., president-elect, Massachusetts Medical Society; David McL. Greeley, M.D., Department of Pediatrics, Boston University School of Medicine; Louis Weinstein, M.D., Division of Medicine, Boston University School of Medicine; Charles A. Janeway, M.D., Department of Pediatrics, Harvard Medical School; James M. Baty, M.D., Department of Pediatrics, Tufts College Medical School; John F. Enders, Ph.D., director of research, Division of Infectious Diseases, Children's Medical Center; Stewart H. Clifford, M.D., district chairman, American Academy of Pediatrics; R. Cannon Eley, M.D., chairman, Massachusetts Chapter, American Academy of Pediatrics; Edward Dyer, M.D., secretary, Massachusetts Chapter, American Academy of Pediatrics; Samuel B. Kirkwood, M.D., commissioner, Massachusetts Department of Public Health; Roy F. Feemster, M.D., director, Division of Communicable Diseases, Massachusetts Department of Public Health; and Johannes Ipsen, M.D., superintendent, Institute of Laboratories, Massachusetts Department of Public Health.

BOOK REVIEW

The Technique of Psychotherapy. By Lewis R. Wolberg, M.D., director, Postgraduate Center for Psychotherapy, and associate clinical professor of psychiatry, New York Medical College. 4°, cloth, 869 pp., New York: Grune and Stratton, 1954. $14.75.

This is a *magnum opus* that represents years of careful work on the part of the author. It is the most complete and thoroughly prepared book of its sort that has ever been published in the United States and one of the most broadly organized and well presented. One wonders how Dr. Wolberg condensed so much in 900 pages.

The book has the advantage of being written by a man who daily does the work he describes. It is not narrow in any secular sense, nor is it particularly limited to any school of psychopathic application. Throughout the volume, it is clear that Dr. Wolberg has lived through the writing of it and thought through the problems while actually struggling with them. It contains much insight and hindsight, and even though the cost is high, compared with that of some texts on this subject, it is crammed with valuable information, demonstrations and explanations that make the purchase well worth while. The references, index and a special section on "Recommended Reading" are particularly valuable.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Pathologic Conferences of Cook County Hospital: Cardiovascular-Renal Problems. Vol. 1. Edited by Hans Popper, M.D., Ph.D., director, Department of Pathology, Cook County Hospital, scientific director, Hektoen Institute for Medical Research of the Cook County Hospital, and associate professor of pathology, Northwestern University Medical School; and Daniel S. Kushner, M.D., associate director of medical education, Cook County Hospital, research associate, Hektoen Institute for Medical Research of the Cook County Hospital, and clinical assistant in medicine and fellow in pathology, Northwestern University Medical School. 8°, cloth, 325 pp., with illustrations. New York: Blakiston Company, 1954. $5.00.

Forty-two persons participated in this conference, which considered cardiac, vascular and renal problems. Short lists of references are appended to the various papers. The lack of an index detracts from the reference value of the book.

Directory for Exceptional Children. Schools, Services, other Facilities. Edited by E. Nelson Hayes, with a preface by M. E. Frampton and E. D. Gall. 12°, paper, 96 pp. Boston: Porter Sargent Publishers, 1954. Paper, $1.10; cloth, $2.20.

This is an important directory. The list emphasizes private schools and facilities, as well as psychiatric and guidance clinics for children.

Symposium on Problems of Gerontology: Proceedings of a symposium held under the auspices of the Johns Hopkins University, School of Hygiene and Public Health and the National Vitamin Foundation, Inc., New York City, March 2, 1954. (Nutrition Symposium Series, No. 9.) By F. H. Bethell, B. F. Chow, C. S. Davidson, H. J. Deuel, Jr., D. J. Ingle, J. E. Kirk, A. I. Lansing, C. N. H. Long, H. A. Rafsky and N. W. Shock. 8°, paper, 141 pp., with tables. New York: National Vitamin Foundation, Incorporated, 1954. $2.50.

This symposium discusses the physiologic and biochemical aspects of aging.

The Epilepsies. Electro-Clinical Correlations. By Henri Gastaut, professor in the Faculté de Médecine de Marseille and chief, Service d'Electrobiologie des Hôpitaux. Translated by Mary A. B. Brazier, neurophysiologist, Massachusetts General Hospital, Boston; with a preface by Wilder Penfield. 8°, cloth, 149 pp., with 21 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $4.75. (*American Lecture Series,* No. 204.)

This special monograph discusses the clinical analysis, etiology, diagnosis and treatment of the epilepsies, the physiological interpretation of epileptic symptoms and anatomic studies, based on the clinical and electroencephalographic observations collected during the past ten years at the laboratory of neurobiology of the Faculty of Medicine at Marseille.

Funktionelle Röntgendiagnostik der Halswirbelsäule. By Dr. C. Buetti-Bäuml, lecturer, Universitäts-Röngeninstitut Basel. 4°, cloth, 160 pp., with 154 illustrations. Stuttgart: Georg Thieme, 1954. DM 42.-($10). (*Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern.)* Vol. 70; (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This is an excellent radiologic atlas of normal and abnormal conditions of the cervical vertebras. A list of references is appended to the text.

Fluid Balance in Surgical Practice. By L. P. LeQuesne, M.A., B.M., B.Ch., (Oxon), F.R.C.S. (Eng.), assistant director, Department of Surgical Studies, Middlesex Hospital. 8°, cloth, 130 pp., with 41 illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $3.50.

This monograph is based on the Moynihan Prize Essay for 1953. The author discusses the theoretical background of fluid and electrolyte exchanges and describes practical methods for dealing with these problems as they arise in clinical surgery. There is a bibliography; the printing was done in England.

The Teaching of Physiology, Biochemistry, Pharmacology. Report of the First Teaching Institute, Association of American Medical Colleges, Atlantic City, October 19-23, 1953. 8°, paper, 196 pp., with 64 tables. Chicago: Association of American Medical Colleges, 1954. (*J. Med. Education,* Vol. 27, No. 7, Part 2. July, 1954.)

Seven papers were read and discussed at the conference on various aspects of the subject. The text is supported by a large amount of documentary material.

The Digital Circulation. By Milton Mendlowitz, M.D., F.A.C.P., associate attending physician, Mount Sinai Hospital, research fellow, Columbia University Division of Goldwater Memorial Hospital, New York City. 4°, cloth, 182 pp., with 60 illustrations and 31 tables. New York: Grune and Stratton, 1954. $6.75.

The author discusses the diseases and related conditions of the peripheral vascular system. The preliminary chapters deal with anatomy, physiology, pharmacology, pathology and methods of diagnosis. The literature has been thoroughly reviewed, and there is a bibliography of 636 titles. There is an index, and the publishing is excellent.

The Optometrist's Handbook of Eye Diseases. By Joseph I. Pascal, M.A., O.D., M.D., director, Eye Department, Stuyvesant Polyclinic, associate ophthalmologist, New York Polyclinic Medical School and Hospital, and lecturer in ophthalmology, New York Polyclinic Medical School and Hospital; and Harold G. Noyes, A.M., M.D., associate in optometry, Columbia University, clinical assistant in ophthalmology, Manhattan Eye, Ear and Throat Hospital, and lecturer in ophthalmology, New York Polyclinic Medical School and Hospital. 8°, cloth, 300 pp., with 155 illustrations and 3 color plates. St. Louis: C. V. Mosby Company, 1954. $9.50.

This book has been written especially for the optometrist, who may well be the first to see the diseased eyes, and also for the student and general practitioner. The authors have been engaged for years in teaching the subject to optometrists, and the text is based on the results of their experiences. The volume is arranged generally by regions of the eye and by diseases and conditions. There is a chapter on the blind and near blind. The publishing is good.

Das Fibrinogen: Seine Bestimmung, seine physiologischen und pathologischen Veränderungen, seine biologische Bedeutung und sein Entstehungsort. By Doz. Dr. med. habil. Friedrich-Horst Schulz, chief physician, Medizinische Universitätsklinik Leipzig. 8°, cloth, 143 pp., with 90 illustrations and 81 tables. Leipzig: VEB Georg Thieme, 1953. DM 17.60 ($4.20).

This monograph deals with the determination, physiology, pathology, biologic importance and means of formation of fibrinogen. Under pathology 55 pages are devoted to the role of fibrin in various diseases of the body. The literature is surveyed, and the references are carried as footnotes to the text. There are indexes of authors and subject.

Biochemistry of Cancer. By Jesse P. Greenstein, chief, laboratory of biochemistry, National Cancer Institute, National Institutes of Health, United States Public Health Service, Bethesda, Maryland. Second edition, revised and enlarged. 8°, cloth, 553 pp., with 176 tables and 41 illustrations. New York: Academic Press, Incorporated, 1954. $12.00.

The author has thoroughly revised this new edition of a valuable book, first published in 1947, to bring it up to date. Extensive lists of references are appended to the chapters. The pertinent literature has been reviewed, and there are indexes of authors and subjects. The book should be in all collections on the subject.

Einrichtung und Arbeitsweise einer Blutbank. By Dr. med. habil. W. Heim, lecturer, Freie Universität Berlin, and chief physician, Surgical Division, Rudolph-Virchow-Krankenhaus, Berlin; and Dr. med. Habil. P. Dahr, professor, Universität Göttingen, and head, Institut für Blutgruppenforschung. 8°, cloth, 328 pp., with 36 illustrations. Stuttgart: Georg Thieme, 1954. DM 33. (Distributed by Intercontinental Medical Book Corporation, New York City.)

The authors give a comprehensive description of the establishment, administration and operation of a blood bank.

Glandular Physiology and Therapy. Prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Fifth edition. 8°, cloth, 611 pp., with 20 illustrations and 42 tables. Philadelphia: J. B. Lippincott Company, 1954. $10.00.

This fifth edition of an important book, the joint work of 31 contributors, has been thoroughly revised and brought up to date. The literature has been reviewed, and extensive bibliographies are appended to the chapters. The book should be in all medical libraries.

Behandlung innerer Krankheiten. Richtlinien und Ratschläge für Studierende und Ärzte. By Prof. Dr. F. Hoff, director, I. Medizinische Universitätsklinik, Frankfurt A.M. Fifth edition. 8°, Bd., 608 pp., 1 table. Stuttgart: Georg Thieme, 1954. DM 55. (Distributed by Intercontinental Medical Book Corporation, New York City.)

This new edition of a standard German textbook first published in 1940 has been thoroughly revised and brought up to date since the fourth edition of 1948. An appendix lists the drugs and therapeutic agents mentioned in the text. There is a good index, and the publishing is excellent.

Atti della Societa Italiana di Cardiologia. XV Congresso tenuto a Viareggio nei giorni 12 e 13 Guigno 1953. Volume II. Communicazioni. Edited by G. Bergamasco. 4°, paper, 320 pp., with illustrations. Milan, Italy: Clinica Medica, 1953. By subscription. (Supplement to Vol. 12 of *Folia cardiologica.*)

The 201 papers read at the congress of the Italian Society of Cardiology are divided into six sections on pericarditis, heart surgery and acquired valvular conditions, electrocardiography, arrhythmia and hypertension and arteriosclerosis.

The Voice of Neurosis. By Paul J. Moses, M.D., assistant clinical professor in charge of speech and voice section, Division of Otolaryngology, Stanford University School of Medicine, San Francisco, California. 8°, cloth, 131 pp., with 4 illustrations. New York: Grune and Stratton, 1954. $4.00.

The author discusses the place of the voice in the diagnosis of neurosis. There is a bibliography of 57 references and a good index.

Refresher Course for General Practitioners: Specially commissioned articles from the British Medical Journal. Second collection, January, 1951, to March, 1952. (Fully revised.) 8°, cloth, 570 pp., with illustrations. London: British Medical Association, 1954. 25 sh.

This second series of 60 articles reprinted from the *British Medical Journal* covers the whole field of medicine and its specialties.

Myokardstoffwechsel und Herztherapie. By Dr. med. Fritz Pendl, chief physician, Internal Division, Kreiskrankenhaus Heidenheim/Brenz. 8°, Bd., 248 pp., with 26 illustrations. Stuttgart: Georg Thieme, 1954. DM 29.70. (Distributed by Intercontinental Medical Book Corporation, New York City.)

This special monograph on myocardial metabolism and the treatment of diseases of the heart surveys the modern literature on the subject. The chapters deal with the structure and energy of the heart muscles, the effect of phosphorus combinations and minerals on energy, edema, heart therapy and albumin, liver and sugar metabolism, and vitamins and hormones in heart therapy. Extensive bibliographies are appended to the chapters, and there are indexes of authors and subjects. The book should be in all collections on the heart.

NONCLINICAL NOTES

APPOINTMENT OF DR. HALSTED

Dr. James A. Halsted has been appointed chief of Professional Services at the Veterans Administration Hospital, Syracuse, New York, and will be associated with the faculty of the State University of New York Upstate Medical School at Syracuse.

NOTICES

PHI DELTA EPSILON LECTURE

The Aaron Brown Lecture of Alpha Omicron chapter of Phi Delta Epsilon Fraternity will be presented by Dr. J. Howard Means, who will speak on the topic "The Need for Experiment in the Social As Well As the Biologic Area of Medicine," in the auditorium, Boston University School of Medicine, on Monday, April 25, at 5 p.m.

MASSACHUSETTS SCHOOL PHYSICIANS' ASSOCIATION

The following program for school physicians will be presented by The Massachusetts School Physicians' Association in co-operation with the Harvard School of Public Health and the Massachusetts Department of Public Health:

April 27. Growth Problems of School Children. Harold C. Stuart, M.D., professor of maternal and child health, Harvard School of Public Health.

May 4. Health Needs of School-Age Children. A Panel Presentation. Moderator: R. Gerald Rice, M.D., director, Division of Maternal and Child Health, Massachusetts Department of Public Health. (Discussion by members of Harvard School of Public Health.)

At the conclusion of the panel on May 4 a business meeting of the association will be held with election of officers.

AMERICAN NEUROLOGICAL ASSOCIATION

The annual meeting of the American Neurological Association will be held at the Palmer House, Chicago, June 13-15.

GEORGE W. GAY LECTURE

The George W. Gay Lecture on Medical Ethics will be held on April 27 at 5:00 p.m. Reverend Dr. George Buttrick will be the speaker. The meeting will be held at the Harvard Medical School, Amphitheater E.

Interested physicians and medical students are invited.

SOCIETY MEETINGS AND CONFERENCES

April. Postgraduate Medical Institute. Page 451, issue of September 9.
April–May. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.
April 22. Boston University Surgical Seminar. Page 603, issue of April 7.
April 23. American Congress of Physical Medicine and Rehabilitation. Page 603, issue of April 7.
April 23. Massachusetts State Society of Medical Technologists. Page 461, issue of March 17.
April 23–29. Industrial Health Conference. Page 509, issue of March 24.
April 25. Yale Medical Society. Page 603, issue of April 7.
April 25. Phi Delta Epsilon Lecture. Notice above.
April 25–28. Consultation Clinics for Crippled Children in Massachusetts. Page 551, issue of March 31.
April 25–30. American College of Allergists. Page 462, issue of March 17.
April 26. Hampden District Medical Society. Page 603, issue of April 7.
April 26. South End Medical Club. Page 603, issue of April 7.
April 26. Harvard Medical Society. Page 509, issue of March 24.
April 26. Alpha Omega Alpha Lecture. Page 554, issue of March 31.
April 26–May 26. Boston City Hospital. House Officers' Lectures. Page 509, issue of March 24.
April 27. Middlesex West District Medical Society. Page 603, issue of April 7.
April 27. George W. Gay Lecture on Medical Ethics. Notice above.
April 27–30. Instituto Nacional de Cardiologia de México. Page 554, issue of March 31.
April 27–May 25. Lahey Clinic Lectures. Page 289, issue of March 17.
April 27–June 15. Boston State Hospital Psychiatry Seminars. Page 461, issue of March 17.
April 27 and May 4. Massachusetts School Physicians' Association. Notice above.
April 28–30. American Goiter Association. Page 329, issue of February 24.
April 30. State University College of Medicine at New York City. Page 289, issue of February 17.
April 30. Phi Delta Epsilon Fraternity. Graduate Club of Boston. Page 461, issue of March 17.
May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
May 6–8. Student American Medical Association. Page 461, issue of March 17.
May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.
May 13 and 14. American Association for Cleft Palate Rehabilitation. Page 461, issue of March 17.
May 13–15. American Academy of Dental Medicine. Page 554, issue of March 31.
May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 18–20. American College of Cardiology. Page 414, issue of March 10.
MAY 23–27. American Trudeau Society. Page 462, issue of March 17.
MAY 29–JUNE 2. American Society of X-Ray Technicians. Page 553, issue of March 31.
JUNE 1–4. American Proctologic Society. Page 648, issue of April 14.
JUNE 1–5. American College of Chest Physicians. Page 553, issue of March 31.
JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
JUNE 6–10. Woman's Auxiliary to the American Medical Association. Page 647, issue of April 14.
JUNE 7–9. United States Public Health Service Medical-Officer Examinations. Page 509, issue of March 24.
JUNE 10–12. American Electroencephalographic Society. Page 647, issue of April 14.
JUNE 13–15. American Neurological Association. Page 689.
JUNE 13–17. European Rheumatology Congress. Page 689.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 28

THURSDAY, APRIL 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. The Use of Function Studies in Pulmonary Resection. Dr. Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*7:00 p.m. Boston City Hospital House Officers' Lecture. Acute Pericarditis. Dr. W. A. Sodeman. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

FRIDAY, APRIL 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, APRIL 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, MAY 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Drs. MacMahon and Baty. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Clinic. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Pharmacology of Vasopressors. Dr. Burnap. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, MAY 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Drs. Patterson, MacMahon and guest. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Soman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic, New England Deaconess Hospital.
*4:30–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Lecture. Physiology of Portal Hypertension. Dr. Charles Child. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, MAY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital. Psychiatry Seminar. Progress in Psychiatric Rehabilitation. Dr. Maxwell Jones. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry. Dr. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15–1:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinic of Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–5:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Anaphylactic Shock in Medicine and Surgery. Drs. John Fromer and J. J. Goodman. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.